SYNTHESIS AND BIOLOGICAL PROPERTIES OF 2-(TETRAHYDROPYRAN-4-YL)THIAZOLES

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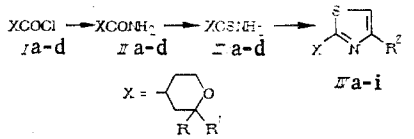
The thiazole ring is the structural basis for several natural and synthetic biologically active compounds. Thiazoles have been investigated as drugs for the treatment of diseases of the central nervous system [1] and other diseases [2, 3].

The present communication describes the synthesis of substituted 2-(tetrahydropyran-4-yl)thiazoles (IVa-i) from tetrahydropyran-4-carboxylic acids (Ia-d) [4, 5]. The latter were converted into their amides (IIa-d), treatment of which with phosphorus pentasulfide gave the thioamides (IIIa-d) (Table 2). Condensation of (IIIa-d) with α-haloketones afforded (IVa-i).



I — IIIa $R = R^1 = CH_3$;
I — IIIb. $R = CH_3$, $R^1 = C_2H_5$; I — IIIc: $R = H$, $R^1 = C_3H_7$-iso,
I — IIId: $R = H$, $R^1 = C_3H_7$;
IVa: $R = R^1 = CH_3$; $R^2 = C_6H_5$; IVb: $R = R^1 = CH_3$, $R^2 = C_6H_4Br$-p;
IVc: $R = R^1 = CH_3$, $R^2 = C_6H_4Br$-p
IVd: $R = R^1 = CH_3 R^2 = C_6H_4Cl$-p; IVe: $R = R^1 = CH_3$,
R^2 = 2,2-dimethyltetrahydropyran-4-yl
IVf. $R = CH_3$, $R^1 = C_2H_5$, $R^2 = C_6H_5$; IVg: $R = H$,
$R^1 = C_3H_7$-iso; $R^2 = C_6H_5$; IVh: $R = H$, $R' = C_3H_7$-iso,
$R^2 = C_6H_4Br$-p IVi: $R = H$, $R^1 = C_3H_7$-iso, $R^2 = C_6H_4Br$-p.

The structures of the resulting thiazoles were established by IR, PMR, and mass spectrometry (Table 1).

EXPERIMENTAL (CHEMISTRY)

IR spectra were obtained on a VP-20 instrument (East Germany), and the PMR spectra on a Varian T-60 spectrometer (USA) with TMS as the standard. Mass spectra were obtained on an MX-1303 instrument, with direct introduction of the sample into the ion source.

2-Alkyl(or dialkyl)tetrahydropyran-4-carboxamides (IIa-d). In a reaction flask was placed 200 ml of dry ether, and gaseous ammonia was introduced with ice-water cooling. A solution of the 2-alkyl-(or dialkyl)tetrahydropyran-4-carbonyl chloride (0.13 mole) in 100 ml of dry ether was then added with stirring in a stream of ammonia, passage of ammonia being continued for a further 30 min at room temperature. Water (30 ml) was added, the amide filtered off, recrystallized from water, and dried in air. The yields and constants of the amides are shown in Table 1.

2-Alkyl(or dialkyl)tetrahydropyran-4-carbothiamides (IIIa-d). In a three-necked flask were placed 200 ml of benzene, 0.32 mole of (IIa-d), and 14.2 g of phosphorus pentasulfide (0.064 mole). The mixture was boiled with vigorous stirring for 10 min, the stirrer stopped, and the hot benzene layer decanted off. A further quantity of benzene was added with stirring, and the mixture was boiled for 20 min followed by decantation. This procedure was

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TABLE 1. 2-(Tetrahydropyran-4-yl)thiazoles (IVa-i)

Compound	Yield, %	bp, °C (mm)	Found, %				Molecular formula	Calculated, %				IR spectrum, cm^{-1} (C–O–C)	PMR spectrum, δ, ppm	Mass spectrum, m/e	mp, °C	
			C	H	N	S		C	H	N	S				hydrobromide	hydrochloride
IVa	78,2	190—191 (3)	70,18	7,16	5,03	11,68	$C_{16}H_{19}ONS$	70,29	7,00	5,12	11,72	1090	7.07–7.93 (m), phenyl, and 5-H of thiazole	273	185,2	163—165
IVb	83,5	221—222 (2,5)	54,61	5,02	4,17	9,24	$C_{16}H_{18}ONSBr$	54,55	5,15	3,97	9,10	1090	7.07–7.78 (m), phenyl and 5-H of thiazole	251, 253	180	132—133
IVc	83,0	219—220 (3)	54,62	5,20	4,12	9,00	$C_{16}H_{18}ONSBr$	54,55	5,15	3,97	9,10	1080	6.93–8.03 (m), phenyl and 5-H of thiazole		180—181	130,5—131
IVd	74,7	218—220 (5)	62,13	5,72	4,44	10,68	$C_{16}H_{18}ONSCl$	61,98	5,89	4,55	10,36	1080			186—187	145—146
IVe	42,1	161—163 (1)	65,89	8,82	4,59	10,00	$C_{17}H_{27}O_2NS$	65,97	8,79	4,52	10,33	1080			—	94—95
IVf	78,0	199—200 (3)	70,88	7,48	4,60	11,03	$C_{17}H_{21}ONS$	71,05	7,36	4,87	11,61	1080	7.03–7.7 (m), phenyl and 5-H thiazole	287	157—158	120—121
IVg	71,1	190—191 (2,5)	71,00	7,29	4,92	10,98	$C_{17}H_{21}ONS$	71,05	7,36	4,87	11,16	1085	7.07–7.78 (m), phenyl and 5-H of thiazole	287	153—155	113—114,5
IVh	51,4	236—237 (3)	55,82	5,59	3,89	8,63	$C_{17}H_{20}ONSBr$	55,74	5,50	3,82	8,75	1090			160—164	64—66
IVi	67,1	239—240 (3,5)	55,86	5,43	3,92	8,60	$C_{17}H_{20}ONSBr$	55,74	5,50	3,82	8,75	1085	6.87–8.05 (m), phenyl and 5-H of thiazole		139—140	103—105

TABLE 2. Amides and Thioamides of 2-Alkyl(or dialkyl)tetrahydropyran-4-carboxylic Acids (IIb-d* and IIIa-d)

Compound	Yield, %	mp, °C	Found, %				Molecular formula	Calculated, %			
			C	H	N	S		C	H	N	S
IIb	75,4	155—156	62,34	10,18	8,29	—	$C_9H_{17}O_2N$	63,12	10,01	8,18	—
IIc	92,4	119—120	63,00	9,88	8,32	—	$C_9H_{17}O_2N$	63,12	10,01	8,18	—
IId	78,8	101	63,40	10,17	8,25	—	$C_9H_{17}O_2N$	63,12	10,01	8,18	—
IIIa	43,3	180—181	55,74	8,95	8,19	18—90	$C_8H_{15}ONS$	55,39	8,72	8,08	18,51
IIIb	44,9	158—159	58,82	9,07	7,56	17,20	$C_9H_{17}ONS$	58,79	9,15	7,47	17,12
IIIc	72,1	78—78,5	58,88	8,87	7,37	16,98	$C_9H_{17}ONS$	58,79	9,15	7,47	17,12
IIId	59,5	—	58,56	9,0	7,30	17,34	$C_9H_{17}ONS$	58,79	9,15	7,47	17,12

*Amide (IIa) has been described previously [4].

repeated twice more. The amide remaining following evaporation of the benzene was recrystallized from alcohol. The yields and constants of the thioamides (IIIa-d) are shown in Table 2.

(Tetrahydropyran-4-yl)-2-thiazoles (IVa-i). In an Erlenmeyer flask was placed a solution of 0.02 mole of the α-bromoketone in 10 ml of acetone, and solution of 0.02 mole of (IIIa-d) in 15 ml of acetone was added. After 5-10 min, the thiazole hydrobromide began to separate (in the case of (IVe) it was necessary to boil the mixture under reflux for 5 h). The hydrobromide was filtered off, washed with ether, and dried in a vacuum desiccator. In order to obtain the free substituted thiazole, the hydrobromide was treated with 20% potassium carbonate solution, extracted with ether, washed with water, and dried over magnesium sulfate. After removal of the ether, the residue was distilled *in vacuo* to give (IVa-i) as colorless or pale yellow viscous liquids.

The hydrochlorides of (IVa-i) were obtained by treatment with ethereal hydrogen chloride. Constants are given in Table 1.

EXPERIMENTAL PHARMACOLOGICAL SECTION

The effects of (IIIa) and (IVa-i) hydrochlorides on the body temperature and behavior of white rats were studied, together with the depressant effects of reserpine. The compounds were administered in doses of 50, 100, and 200 mg/kg. The skin temperature was measured before administration of the compounds, and 1, 3, 5, and 24 h later. Narrowing of the eyelid slit (blepharoptosis) was determined by the method described in [6]. Supression of spontaneous motor activity was expressed in points [7]. Occurrence of catalepsy was established by the duration of maintenance of the animals on a vertical mesh, four corks, and cross bars at heights of 3 and 6 cm for mice, and 3, 9, and 14 cm for rats [8].

In order to study their effects on reserpine, the compounds were administered to rats in a dose of 100 mg/kg subcutaneously (compounds (IV and g) in doses of 10 and 200 mg/kg subcutaneously), 30 min before administration of the neuroleptic (2 mg/kg). In a series of experiments, (IVa) and (IVg) were administered in a dose of 100 mg/kg 1 and 2 h following administration of reserpine. Compounds (IVa) and (IVg) were selected for detailed study.

In experiments on mice, the effects of (IVa) and (IVg) were studied on the effects of reserpine in the presence of a monoamine oxidase (MAO) inhibitor. The MAO inhibitor, pyrazid, was administered in a dose of 5 mg/kg 18 h before administration of the compounds under study (100 mg/kg), and the reserpine (1 mg/kg) was administered 30 min later.

The antiserotonin activities of (IVa) and (IVg) were studied by administering them to mice in a dose of 50 mg/kg 45 min before injection of indopan (5 mg/kg). Thirty minutes after the injection, the animals received 5-hydroxytryptophan (5-HT) in a dose of 50 mg/kg intraperitoneally. The number of shaking movements of the head was recorded over a period of 30 min following administration of 5-HT [9].

To study the effects on the hypothermic effects of DOPA (3,4-dihydroxyphenylalanine), (IVa) and (IVg) were administered to mice in a dose of 100 mg/kg 30 min before intraperitoneal administration of dl-DOPA (300 mg/kg). The skin temperature was measured before treatment with dl-DOPA, and $\frac{1}{2}$, 1, 2, and 3 h later.

Instead of the test compounds, the control animals received physiological saline. The results were treated by the Student—Fisher method.

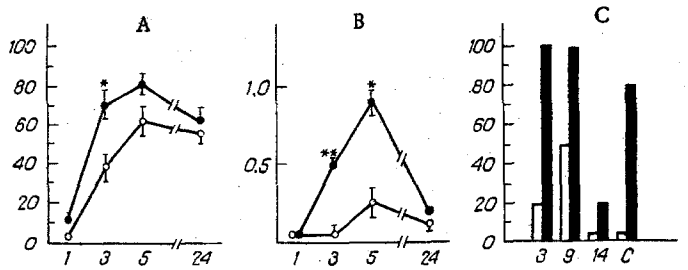

Fig. 1. Effect of (IVg) on the depressant effects of reserpine: blepharoptosis (A), suppression of spontaneous motor activity (B), and catalepsy (C). Abscissae: A and B, time of observation (h); C, type of catalepsy. Ordinates: A, increase in blepharoptosis (%); B, suppression of spontaneous motor activity (in points); C, extent of catalepsy (%). The black circles and columns denote animals receiving (IVg) before administration of reserpine, and the light circles and columns the control animals. The vertical lines represent the standard errors. One asterisk — $P < 0.02$; two asterisks — $P < 0.05$.

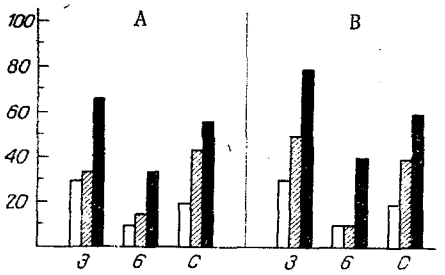

Fig. 2. Effects of (IVg) (A) and (IVa) (B) on reserpine catalepsy five hours after administration. Abscissae: type of catalepsy. Ordinates: extent of catalepsy (%). Light columns — control animals; shaded columns, animals receiving (IVa) or (IVg) before administration of reserpine; black columns, animals with previously inhibited MAO.

The acute toxicity of (IVa) and (IVg) was determined in white mice by the intraperitoneal route, and the LD_{50}'s were calculated by the Litchfield-Wilcoxon method. The LD_{50} of (IVa) was 579 (561.04-597.53) mg/kg, and of (IVg), 500 (442.46-565.0) mg/kg.

The white mice used in the experiments weighed 18-22 g, and the white rats 150-180 g, of both sexes, each group containing 5-10 animals.

Results and Discussion. The test compounds, when administered to rats in doses of 50-200 mg/kg, slightly increased spontaneous motor activity and tactile sensitivity, caused slight exophthalmia, and had no effect on the body temperature of the animals.

Compounds (IIIa) and (IVb-f, g, and i) did not noticeably modify the effects of reserpine.

Following the preliminary administration of (IVa) and (IVg) to rats in doses of 10, 100, and 200 mg/kg, a significant increase was observed in the depressant effects of reserpine (blepharoptosis, suppression of spontaneous motor activity, and catalepsy) (Fig. 1). A slight increase in the cataleptogenic effects of the neuroleptic was observed following administration of (IVg) in a dose of 100 mg/kg, 1 and 2 h after administration of reserpine. Potentiating effects on reserpine can be caused by compounds which activate MAO, this effect being more marked following preliminary inhibition of the enzyme. As will be seen from Fig.

2, in mice which had previously received pyrazid, (IVa) and (IVg) in a dose of 100 mg/kg increased suppression, blepharoptosis, and catalepsy induced by reserpine to a greater extent than in the control animals which had not received the MAO inhibitor.

5-HT, when administered to mice in a dose of 50 mg/kg, did not cause head tremor, but in those which had received 5-HT following treatment with indopan, an average of 25-35 tremors was observed over a period of 30 min. When (IVa) or (IVg) was administered before treatment with indopan, the number of tremors decreased by 82% ($P < 0.001$), and 67% ($P < 0.01$) respectively Compound (IVa), administered after 30 min, had no significant effect on the hypothermic effect of dl-DOPA. For a period of i h, (IVg) prevented the development of the hypothermic effects of dl-DOPA ($P < 0.001$).

This investigation has shown that the most active compounds are those with dimethyl (IVa) and isopropyl (IVg) radicals in the 2-position of the tetrahydropyran ring.

Compounds (IVa) and (IVg) prevented the development of the effects of 5-HT and dl-DOPA. Antagonism towards the precursors of serotonin and catecholamines can be due to blockage of receptors, inhibition of synthesis, or increased metabolism of amines. Potentiation of the depressant effects of reserpine, especially when the MAO is first inhibited, suggests that (IVa) and (IVg) may have an activating effect on deamination. Similar results have been obtained previously, in a study of the mono- and dihydrazides of 2-methylindolyl-3-propionic acids [10, 11].

The search for new compounds capable of inceasing the activity of the enzyme holds promise in view of recent reports on the decreased activity of MAO in some psychiatric conditions and somatic diseases [12, 13].

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