SYNTHESIS AND HYPOLIPIDEMIC ACTIVITY OF 3-(4-THIAZOLYL)-6-ALKYL-7-ALKOXYCHROMANONES

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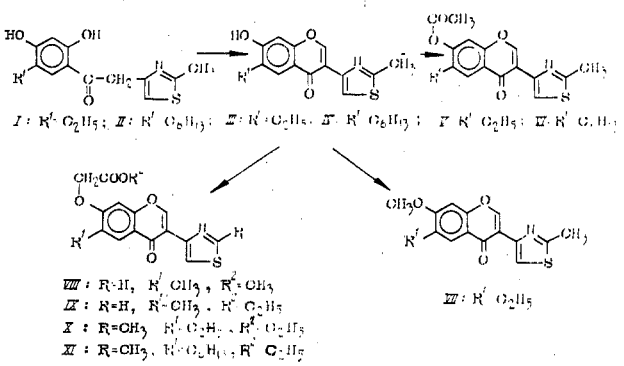
Some flavonoid compounds are known to possess vitamin P or antitumor activity, while others stimulate the activity of cardiac muscle [1]. Natural isoflavonoids and their synthetic analogs possess hypolipidemic and antiarteriosclerotic acitivity [2-6]. There have also been reports of pharmacological activity in heterocyclic derivatives of chromanones [7-10]. In the search for compounds active in the cardivascular system, we have synthesized some 3-(4-thiazoyl)-6-alkyl-7-hydroxychromanones and have studied their reactions with alkylating, acylating, nucleophilic, and electrophilic reagents, together with their hypolipidemic activity.

The α-(2-methyl-4-thiazolyl)-1,4-dihydroxy-5-alkylacetophenones required for the synthesis of these chromanones were obtained by condensing the appropriate thiazolylacetonitriles with 4-alkylresorcinols in boron trifluoride etherate in the presence of dry hydrogen chloride. The structures of ketones (I) and (II) were confirmed by their PMR spectra, which showed discrete absorption for the aromatic (3-H and 6-H) and hydroxyl (2-OH and 4-OH) protons. The 2-OH groups were involved in the formation of intramolecular hydrogen bonds and gave signals at low field (δ 12.05-12.26 ppm). The 4-OH groups formed intermolecular hydrogen bonds, or a hydrogen bond with the solvent (DMSO), and hence their protons gave signals in the range of δ values 10.35-10.56 ppm. Ketones (I) and (II) form colored chelate complexes with ferric chloride solution, which also provides confirmation of the participation of the 2-OH groups in the formation of intramolecular hydrogen bonds.



Thiazole analogs of the naturally occurring 6-alkyl-7-hydroxyisoflavones (III) and (IV) were formed in high yields by reaction of the ketones (I) and (II) with ethyl orthoformate in pyridine, in the presence of catalytic amounts of piperidine. Compounds (III) and (IV) were purified as their acetyl derivatives, then deacetylated to the free 7-hydroxychromanones.

The 7-hydroxychromanones (III) and (IV) readily form derivatives at the phenolic hydroxyl (V-XI) on treatment with acetic anhydride, dimethyl sulfate, and methyl and ethyl bromoacetates in the presence of bases. 3-(4-Thiazolyl)-6-alkyl-7-hydroxychromanones and their derivatives (III-XI) are colorless crystalline solids with high melting points, readily soluble in organic solvents and sparingly soluble in water. Their structures were confirmed by their elemental analyses and PMR spectra (Table 1).

Certain pyrazoles are known to possess antiinflammatory activity, and Mannich bases of flavonones [11] and isoflavonones [12] affect the activity of the central nervous system. For this reason, we have synthesized analogous compounds based on thiazole analogs of isoflavonones.

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TABLE 1. Properties of 3-(4-Thiazolyl)-6-alkylchromanones

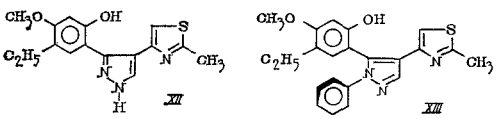
Compound	Yield, %	Mp, °C	Found, % S	Molecular formula	Calculated, % S	PMR spectral data, δ, ppm						
						protons of the chromanone ring					protons of the thiazole ring	
						2-H	5-H	6-R	7-R	8-R	2-R	5-H
III	72	234—5	11,30	$C_{15}H_{13}NO_3S$	11,16	8,94	7,91	CH_3CH_2 — 1,23; 2,71	OH 10,83	H 6,97	CH_3 2,78	8,38
IV	75	204—5	9,05	$C_{19}H_{21}NO_3S$	9,34	8,92	7,90	C_6H_{13} —	OH 10,73	H 7,01	CH_3 2,77	8,38
V	86	173—4	10,03	$C_{17}H_{15}NO_4S$	9,73	8,89	8,13	CH_3CH_2 — 1,28; 2,65	$OCOCH_3$ 2,38	H 7,21	CH_3 2,73	8,30
VI	85	147	8,31	$C_{21}H_{23}NO_4S$	8,32	8,74	7,97	$CH_3C_4H_8CH_2$ — 0,90; 1,35	$OCOCH_3$ 2,37	H 7,08	CH_3 2,71	8,15
VII	87	182—3	10,77	$C_{16}H_{15}NO_3S$	10,64	8,91	7,88	CH_3CH_2 — 1,20	OCH_3 3,99	H 7,11	CH_3 2,76	8,26
III	89	196—7	9,70	$C_{16}H_{13}NO_5S$	9,68	8,74	7,86	CH_3 — 2,37	OCH_2COOCH_3 4,68; 3,80	H 7,08	H 8,56	8,40
IX	82	180—1	9,49	$C_{17}H_{15}NO_5S$	9,28	8,82	7,95	CH_3 — 2,43	$OCH_2COOCH_2CH_3$ 4,73; 4,33; 1,35	H 6,62	H 8,67	8,49
X	90	101—2	8,82	$C_{19}H_{19}NO_5S$	8,59	8,79	8,02	CH_3CH_2 — 1,39; 2,89	$OCH_2COOCH_2CH_3$ 4,77; 4,37; 1,39	H 6,66	CH_3 2,85	8,32
XI	81	95	7,35	$C_{23}H_{27}NO_5S$	7,46	8,61	7,82	$CH_3C_4H_8CH_2$ — 0,91; 1,34; 2,64	$OCH_2COOCH_2CH_3$ 4,62; 4,22; 1,34	H 6,49	CH_3 2,72	8,15
XVI	73	155—6	8,37	$C_{17}H_{18}N_2O_3S$	8,47	8,61	7,76	CH_3 — 2,32	OH 8,45	$CH_2N(CH_3)_2$ 3,93; 2,45	CH_3 2,72	8,14
XV	82	138—9	9,26 N 8,15	$C_{18}H_{20}N_2O_3S$	9,30 N 8,13	8,65	7,82	CH_3CH_2 — 1,30	OH 11,82	$CH_2N(CH_3)_2$ 3,93; 2,44	CH_3 2,73	8,19
XVI	82	200—1	Br 21,80	$C_{16}H_{12}BrNO_3S$	Br 21,82	9,03	7,90	CH_3CH_2 — 1,22	OH	Br	CH_3 2,79	8,35

Note: The PMR spectra of (III, IV, VII, XVI) were measured in DMSO, and the remaining compounds in deuterochloroform, using a ZKR-60 instrument (Czech SSR), relative to TMS (internal standard).

TABLE 2. Effect of 3-(4-Thiazolyl)-6-alkyl-7-alkoxychromanones on Hyperlipidemia in Rats (n=6), Induced by Administration of Triton WR-1339

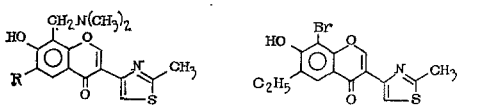
Treatment	Blood serum cholesterol and triglyceride levels in rats			
	cholesterol	triglycerides	relative to the control, %	
	mg % (M ± m)		cholesterol	triglycerides
Triton	284,9±12,3	388,9±8,5		
V + triton	273,0±10,0	275,5±4,4	—4,0	—29,1
VI + triton	249,3±5,1	258,0±11,2	—12,5	—33,6
VII + triton	266,1±9,6	327,8±2,2	—6,6	—15,8
VIII + triton	210,8±3,9	271,2±2,7	—26,0	—30,3
XI + triton	290,6±5,6	276,5±7,1	—	—29,0
X + triton	288,1±6,2	362,5±2,7	—	—7,0
XI + triton	272,0±5,3	250,0±5,4	—4,6	—35,7
Cetamyfen + Triton	251,1±5,5	327,0±8,9	—11,9	—16,0

Note: $P < 0.001$.



XII

XIII



XIV: R = CH_3, XV: R = C_2H_5 XVI

The 7-methoxychromanone (VII) cyclizes with hydrazine hydrate or phenylhydrazine to give the corresponding pyrazoles (XII) and (XIII), the structures of which are confirmed by their chemical reactions and PMR spectra [13]. Compounds (XII) and (XIII) are readily soluble in 2N sodium hydroxide, indicating the presence of a phenolic hydroxyl in the molecule. The pyrazole (XII) gives a bluish-green coloration with alcoholic ferric chloride, as a result of the formation of a chelate with the participation of the phenolic hydroxyl and the nitrogen atom of the pyrazole ring. In the case of (XIII), the formation of such a chelate complex is not possible. The pyrazole structure of (XII) and (XIII) is shown by separate occurrence of singlets in the PMR spectra for the 2-OH and NH groups, together with the shift of the signal for the 6-H proton to higher field by 1 ppm as compared with the position of the peak for the 5-H proton in the original methoxychromanone (VII). The proton of the phenolic hydroxyl in the recyclization product (XIII) appears in the PMR spectrum as a narrow peak at δ 10.59 ppm, confirming the absence of intramolecular interactions between the nitrogen atom of the pyrazole ring and the hydroxyl. The five-proton singlet for the protons of the phenyl group at 7.38 ppm indicates that the benzene ring attached to the nitrogen atom departs from the plane of the pyrazole ring.

Reaction of the thiazole analogs of 6-methyl- [14] and 6-ethyl-7-hydroxyisoflavonone (III) with bisdimethylaminomethane in dioxan solution with heating affords the Mannich bases (XIV) and (XV). The dimethylamino group and the bromine atom [in the case of bromination in acetic acid of the chromanone (VII)] enter in the 8-position of the chromanone ring. There is no signal for an 8-H proton in the PMR spectra of derivatives (XIV-XVI).

Table 2 shows the influence of 3-(4-thiazolyl)-6-alkyl-7-hydroxychromanones on hyperlipidemia in rats. It may be concluded from Table 2 that in hyperlipidemia induced by Triton WR-1339, administration of (V-XI) to experimental animals results in a delay in the development of hyperlipidemia, a decrease in cholesterol and especially triglycerides in comparison with currently-used drug cetamyfen. This is particularly noticeable in the case of (VI) and (VIII). These results indicate that heterocyclic analogs of isoflavin hold promise in the search for new drugs for the treatment of arteriosclerosis.

EXPERIMENTAL (PHARMACOLOGICAL)

Hyperlipidemic activity was measured in white male Wistar rats weighing 200-300 g receiving a standard diet, with experimental hyperlipidemia induced by administration of Triton WR-1339. The test compounds were

administered intraperitoneally in a dose of 150 mg/kg* 24 h before administration of Triton, and at the same time. Triton was administered intraperitoneally in a dose of 225 mg/kg. For purposes of comparison, the drug cetamyfen (200 mg/kg) was studied. The LD_{50} was determined in mice by the intraperitoneal route. No toxic effects were noted at a dose of 3000 mg/kg. Total cholesterol [15] and triglycerides [16] were measured in the blood serum. The experimental results were evaluated statistically.

EXPERIMENTAL (CHEMICAL)

α-(2-Methyl-4-thiazolyl)-2,4-dihydroxy-5-ethylacetophenone (I). A rapid stream of dry hydrogen chloride was passed through a solution of 12.96 g (94 mmole) of 4-ethylresorcinol and 12.96 g (94 mmole) of 2-methyl-4-thiazolylacetonitrile in 70 ml of boron trifluoride etherate, with stirring and heating at 50-60°C, for 10 h. The reaction mixture was then kept overnight at 20°C, and 600 ml of water was added, the mixture boiled for 2 h, and the pH adjusted to 3.0 by the addition of ammonia. The resulting precipitate was filtered off to give a yield of 19.2 g (71%) of colorless needles, mp 175°C (from alcohol). Found: S 11.72; N 5.06. $C_{14}H_{15}NO_3S$. Calculated %: S 11.56; N 5.05. PMR spectrum in DMSO, δ, ppm: CH_2 4.38; 2-OH 12.26; 3-H 6.34; 4-OH 10.56; 6-H 7.72; thiazole ring protons: 2-CH_3 2.64; 5-H 7.25.

α-(2-Methyl-4-thiazolyl)-2,4-dihydroxy-5-hexylacetophenone (II). A rapid stream of dry hydrogen chloride was passed through a mixture of 1.94 g (10 mmole) of 4-hexylresorcinol and 1.38 g (10 mmole) of 2-methyl-4-thiazolylacetonitrile in 30 ml of boron trifluoride etherate with stirring for 12 h at 50-60°C. The reaction mixture was kept for one day at 20°C, then 170 ml of hot water was added and the mixture boiled for 2 h, and the pH adjusted to 3.0-4.0 with ammonia. The precipitate which separated was filtered off. Yield 1.9 g (60%), colorless needles mp 112-113°C (from aqueous alcohol). Found, %: S 9.84. $C_{18}H_{23}NO_3S$. Calculated %: S 9.61. PMR spectrum in DMSO, δ, ppm: CH_2 4.32; 2-OH 12.05; 3-H 6.20; 4-OH 10.35; 6-H 7.59; thiazole ring protons: 5-H 7.10.

3-(2-Methyl-4-thiazolyl)-6-ethyl-7-hydroxychromanone (III). A mixture of 35 g (134 mmole) of the ketone (I), 134 ml of pyridine, 67 ml of ethyl orthoformate, and 1.5 ml of piperidine was heated at 120-130°C for 6 h. Completion of the reaction was determined by TLC on Silufol plates in the system benzene–ethanol (9:1). The reaction mixture was added to ice water, and the resulting precipitate filtered off and crystallized from alcohol. Yield, 27.8 g.

3-(2-Methyl-4-thiazolyl)-6-hexyl-7-hydroxychromanone (IV). A mixture of 30 g (95 mmole) of the ketone (II), 42 ml of ethyl orthoformate, 93 ml of pyridine, and 1 ml of piperidine was heated at 120-130°C for 7 h. The reaction mixture was poured into ice water, and the precipitate washed repeatedly with ice water and crystallized from alcohol. Colorless needles, yield 24.4 g.

3-(2-Methyl-4-thiazolyl)-6-ethyl-7-acetoxychromanone (V). To a hot solution of 0.57 g (2 mmole) of the chromanone (III) in 5 ml of dry pyridine was added 1.02 g (10 mmole) of acetic anhydride, and the mixture kept for one day at 20°C. The product was filtered off and washed on the filter with water followed by alcohol. Crystallization from benzene gave 0.56 g of colorless crystals.

3-(2-Methyl-4-thiazolyl)-6-hexyl-7-acetoxychromanone (VI). A mixture of 20 g (58 mmole) of the chromanone (IV), 33 ml (350 mmole) of acetic anhydride, and 50 ml of pyridine was boiled for 2 h. The precipitate which separated on cooling was crystallized from toluene to give colorless needles, yield 19.1 g.

3-(2-Methyl-4-thiazolyl)-6-ethyl-7-methoxychromanone (VII). To a solution of 0.57 g (2 mmole) of the chromanone (III) in 30 ml of dry acetone was added 0.28 g (2.2 mmole) of dimethyl sulfate and 0.83 g (6 mmole) of freshly ignited potassium carbonate, and the mixture was boiled for 4 h. The precipitate of inorganic salts was filtered off, the solvent removed, and the residue crystallized from alcohol. Colorless needles, yield 0.52 g.

3-(2-Methyl-4-thiazolyl)-6-ethyl-7-ethoxycarbonylmethylmethoxychromanone (X). To a solution of 0.57 g (2 mmole) of the chromanone (III) in 30 ml of dry acetone was added 0.67 g (4 mmole) of ethyl bromoacetate and 0.83 g (6 mmole) of potassium carbonate, and the mixture was boiled for 3-5 h. The precipitate was filtered off, the solvent distilled off, and the residue crystallized from alcohol. Colorless needles, yield 0.67 g.

Compounds (VIII) and (IX). These were obtained in a similar way to (X), from 10 mmole of 3-(4-thiazolyl)-6-methyl-7-hydroxychromanone [14], 20 mmole of methyl or ethyl bromoacetate, and 30 mmole of potassium carbonate.

* In order to minimize toxic effects of the drugs on prolonged administration, the optimum dose was taken as 1/20 of the LD_{50}. Further reduction of the dose resulted in the compounds losing their effectiveness.

3-(2-Methyl-4-thiazolyl)-6-hexyl-7-ethoxycarbonylmethoxychromanone (XI). A solution of 2 g (5.8 mmole) of the chromanone (IV) and 1.2 ml (12 mmole) of ethyl bromoacetate in 50 ml of dry acetone was boiled with 3.24 g (17.4 mmole) of potassium carbonate for 3 h. The hot solution was filtered, the solvent evaporated, and the residue washed with cold alcohol and crystallized from alcohol. Colorless needles, yield 2 g.

3-(2-Hydroxy-4-methoxy-5-ethylphenyl)-4-(2-methyl-4-thiazolyl)pyrazole (XII). The chromanone (VII) (1 mmole) was dissolved with heating in the minimum amount of alcohol, and 6 ml of a 2 N solution of hydrazine hydrate in alcohol was added. After 5-10 min, the reaction mixture was diluted with water to 100-120 ml, and the precipitate which separated was filtered off. Yield 93%, mp 196-197°C (from aqueous alcohol). Found, %: N 13.59. $C_{16}H_{17}N_3O_2S$. Calculated %: N 13.32. PMR spectrum in DMSO, δ, ppm: protons of the phenolic moiety of the molecule: 2-OH 12.60; 3-H 6.45; 4-OCH_3 3.73; 5-CH_2H_5 1.10; 6-H 6.91; pyrazole ring protons: NH 9.80; 5-H 7.76; thiazole ring protons: 2-CH_3 2.68; 5-H 6.81.

1-Phenyl-4-(2-methyl-4-thiazolyl)-5-(2-hydroxy-4-methoxy-5-ethylphenyl)pyrazole (XIII). A mixture of 0.6 g (2 mmole) of the chromanone (VII) and 0.65 g (6 mmole) of phenylhydrazine in 10 ml of alcohol was heated at 100-110°C for 15 h. The reaction mixture was poured into 50 ml of water, and the precipitate filtered off. Yield 0.54 g [70%, mp 211°C (dec.)]. Found, %: S 8.18. $C_{22}H_{21}N_3O_2S$. Calculated %: S 8.19. PMR spectrum in DMSO, δ, ppm: protons of the phenolic moiety of the molecule: 2-OH 10.59; 3-H 6.63; 4-OCH_3 3.93; 6-H 6.93; pyrazole ring protons: 1-C_6H_5 7.38; 3-H 8.17; thiazole ring protons: 5-H 6.65.

3-(2-Methyl-4-thiazolyl)-6-methyl- (XIV) and 3-(2-Methyl-4-thiazolyl)-6-ethyl-7-hydroxy-8-dimethylaminomethylchromanone (XV). A mixture of 2 mmole of the chromanone and 1 ml of bisdimethylaminomethane in 10 ml of dioxane was boiled for 3 h. The dioxane and excess reagent were distilled off under a water pump vacuum. The products obtained were crystallized from acetonitrile.

3-(2-Methyl-4-thiazolyl)-6-ethyl-7-hydroxy-8-bromochromanone (XVI). To a suspension of 0.57 g (2 mmole) of the chromanone (III) in 6 ml of glacial acetic acid was added gradually with stirring and heating (70-80°C) 0.32 g (2 mmole) of bromine in 4 ml of glacial acetic acid. Stirring was continued for 4 h. The precipitate was filtered off and crystallized from aqueous alcohol or acetic acid.

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