THE SEARCH FOR RADIOPROTECTORS AMONG KETOCOMPOUNDS

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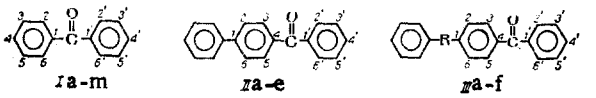
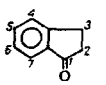
In a search for new radioprotectors and the determination of the role of the ketone group in the activity of the molecule, we synthesized or isolated 42 substances from plant raw materials. According to the existing concepts, ketones can inhibit processes of migra-



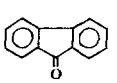
Ia-m

IIa-e

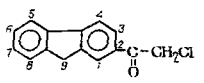
IIIa-f



IVa-b



V



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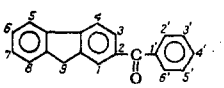
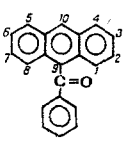
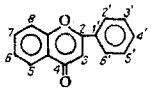


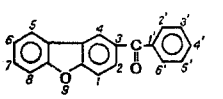
VIIa-c



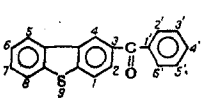
VIII



IXa-d



X



XIa-c

Ia: $R^4 = R^{4'}Cl$

Ib: $R^4 = Cl$; $R^{4'} = CH_3$

Ic: $R^3 = Cl$; $R^{4'} = CH_3$

Id: $R^2 = Cl$; $R^{4'} = CH_3$

Ie: $R^2 = OH$; $R^{4'} = CH_3$

If: $R^3 = OCH_3$; $R^{4'} = CH_3$

Ig: $R^4 = OCH_3$; $R^{4'} = CH_3$

Ih: $R^3 = R^4 = R^{4'} = CH_3$

Ii: $R^3 = R^4 = R^{4'} = CH_3$; $R^6 = SO_3Na$

Ij: $R^4 = CH_2Cl$; $R^{3'} = R^{4'} = CH_3$

Ik: $R^4 = OCH_3$; $R^{2'} = R^{4'} = CH_3$

Il: $R^3 = R^4 = R^{4'} = CH_3$; $R^5 = NO_2$

Im: $R^4 = OCH_3$; $R^{4'} = OC_2H_5$

IIa, V, VI, VIIa, VIII, XII, XIII: R = H

IIb: $R^{3'} = Cl$

IIc: $R^{2'} = Cl$

IId: $R^{2'} = CH_3$

IIe: $R^{4'} = CH_3$

IIIa: $R = CH_2-CH_2$

IIIb: $R = CH_2-CH_2$; $R^{2'} = Cl$

IIIc: $R = CH_2-CH_2$; $R^{3'} = Cl$

IIId: $R = CH_2-CH_2$; $R^{4'} = Cl$

IIIe: $R = CH_2$; $R^{4'} = Cl$

IIIf: $R = CH-CH_3$; $R^{4'} = Cl$

IVa: $R^2 = CH_3$; $R^5 = OH$

IVb: $R^2 = CH_3$; $R^5 = ONa$

VIIb: $R^{3'} = Cl$

VIIc: $R^{4'} = OCH_3$

IXa: $R^3 = R^5 = R^7 = R^{4'} = R^{5'} = OH$

$R^{3'}$ = O-Glucosyl

IXb: $R^5 = R^7 = R^{3'} = R^{4'} = OH$

R^3 = O-Glucosyl

IXc: $R^3 = R^5 = R^{3'} = R^{4'} = OH$

R^7 = O-Glucosyl

IXd: $R^5 = R^{4'} = OH$

$R^3 = R^7$ = O-Rhamnosyl

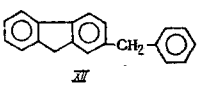
X: $R^{4'} = Cl$

XIa: $R^{3'} = Br$

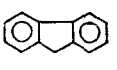
XIb: $R^{4'} = NO_2$

XIc: $R^{2'} = R^{4'} = Cl$

Hydrocarbons



XII



XIII

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tion of energy and elementary particles during irradiation [7, 15], which may promote protection against radiation [4, 14]. In this work radioprotectors were selected among diaryl and polycyclic ketones and hydrocarbons. In this case, according to the data of [4], an important place among the substances studied is occupied by benzophenone derivatives.

Most of the ketones were produced by acylation of the corresponding hydrocarbons and their derivatives with acid chlorides under the conditions of the Friedel-Crafts reaction, using small amounts either of ferric chloride or of zinc chloride (0.1-10 mmoles per mole of the acid chloride). The synthesis and characteristics of benzophenone derivatives (Ia-m) were cited in [1, 11], benzoyldiphenyl (IIa-e), benzoyldibenzyl (IIIa-d), benzoyldiphenylmethane (IIIe), and benzoyldiphenylethane (IIIf) in [12, 13]. Ketone-containing derivatives of indan (IVa-b), fluorene (V, VI), benzoylfluorene (VIIa-c), and benzoylanthracene (VIII) were synthesized according to [2, 3, 10]. The flavonol glycosides IXa-d were isolated from plants of the family Malvaceae [5, 6, 8].

EXPERIMENTAL CHEMISTRY

3-(4'-Nitrobenzoyl)dibenzothiophene (XIb). Dibenzothiophene (1.84 g, 10 mmoles) was heated with 1.85 g (10 mmoles) of p-nitrobenzoyl chloride and 0.02 g (0.1 mmole) ferric chloride for 1 h at a temperature of 170-180°C. The mixture was dissolved in benzene, washed with a 10% solution of alkali, with water, and dried. The benzene solution was passed through a column with aluminum oxide, eluent benzene. The benzene was distilled off and the residue recrystallized from glacial acetic acid. Yield 73%, mp 125°C. Thin-layer chromatography on aluminum oxide in the system chloroform–hexane (4:1) gives one spot with R_f 0.83. Found, %: C 69.10; H 3.12; N 3.97. $C_{19}H_{11}NO_3S$. Calculated, %: C 68.47; H 3.30; N 4.20. Molecular weight 333 by mass spectrometry. IR spectrum, ν_{max}, cm^{-1}: 1605 (aromatic system of dibenzothiophene); 1655 (C–O); 1525 (C–NO_2).

3-(2',4'-Dichlorobenzoyl)dibenzothiophene (XIc). Dibenzothiophene (1.84 g, 10 mmoles) was heated with 2.1 g (10 mmoles) of 2,4-dichlorobenzoyl chloride and 0.02 g (0.1 mmole) ferric chloride for 1 h at the temperature 170-180°C. The reaction product was distilled under vacuum, collecting the fraction at 275-280°C/3 mm Hg. After its recrystallization from alcohol, the mp was 123°C. R_f 0.47 under the conditions of thin-layer chromatography described above. Found, %: C 63.90; H 2.62; Cl 19.99. $C_{19}H_{10}CCl_2S$. Calculated, %: C 64.04; H 2.80; Cl 19.66. Molecular weight 356 by mass spectrometry. IR spectrum, ν_{max}, cm^{-1}: 1590 (aromatic system of dibenzothiophene); 1675 (C=O), 730, 740 (C–Cl).

The position of the 3,4'-nitrobenzoyl and 2',4'-dichlorobenzoyl groups was established by the PMR method according to the shift of the signal of the C_4 proton in the weak field direction in comparison with the signals of the C_4 and C_5 protons in dibenzothiophene, analogously to the procedure described for 3-benzoyldibenzothiophene [9].

EXPERIMENTAL BIOLOGY

The experiments were conducted on 1470 C57Bl/6 mice of both sexes, with an initial age of 3.5-4 months and an initial weight of 18-20 g. The substances were injected intraperitoneally in a volume of 0.2 ml of liquid per mouse. Compounds sparingly soluble in water were suspended in a Tween–water mixture (1:9). In a study of the acute toxicity, the lethal dose LD_{50} causing death of 50% of the animals was determined. For most of compounds it could not be determined on account of the poor solubility and low toxicity of the substances. In this case the limit of testing was the amount that could be introduced with a syringe. In a study of the radioprotective properties, the compounds were introduced in amounts of one-third of LD_{50}; or the maximum amount of the substance that, according to preliminary investigations was absorbed from the abdominal cavity in a period of seven days, was tested.

The mice were irradiated on an IGUR-1 cesium γ setup once at a dose rate of 1.2 cGy/sec. The substances were administered to the mice 15 min and 3 h before irradiation. The lethal dose of irradiation, corresponding to 95-99% death of the mice in 30 days ($LD_{(95-99)/30}$), was 810 cGy for males and 855 cGy for females. The radioprotective effect was judged from the 30-day survival of the mice.

The toxic and radioprotective properties of the substances studied are presented in Table 1.

As can be seen from the table, 29 compounds (Ia, e, i, m, IIa-e, IIIa-f, V, VIIa-c, VIII, IXa-d, X, XIa-c, XIII) did not cause death of mice in 1000-2000 mg/kg, which may be associated with their low accessibility in view of their poor solubility.

TABLE 1. Toxic and Radioprotective Properties of the Substances I-XII Studied

Compound	Toxicity (LD_{50}, mg/kg)	Radioprotective properties		
		amount of substance, mg/kg	survival, %	number of mice
Time of administration 15 min before irradiation				
Ia	Nontoxic, 1500	500	15±8	20
Ib	470	155	0	15
Ic	800	270	7±6	15
Id	360	120	7±6	15
Ie	Nontoxic, 1500	50	33±12	15
If	1100	370	7±6	15
Ig	550	180	0	15
Ih	2000	650	7±6	15
Ii	Nontoxic, 2000	1000	13±9	15
Ij	300	100	7±6	15
Ik	500	170	0	20
Il	620	207	13±9	15
Im	Nontoxic, 1500	500	5±5	20
IIa	Nontoxic, 2000	660	50±16*	10
IIb	The same	660	37±11*	20
IIc	» »	660	10±6	25
IId	Nontoxic, 1000	400	0	15
IIe	Nontoxic, 2000	660	40±11**	20
IIIa	Nontoxic, 1000	1000	0	15
IIIb	The same	800	0	15
IIIc	» »	800	0	15
IIId	» »	200	0	15
IIIe	» »	200	0	15
IVa	430	140	43±8**	85
IVb ***	670	225	20±7	35
V	Nontoxic, 2000	500	53±13**	15
VI	340	110	30±10*	20
VIIa	Nontoxic, 2000	500	25±10	20
VIIb ***	The same	500	35±11*	20
VIIc	» »	500	45±11**	20
VIII	» »	500	10±7	20
IXa	» »	400	60±10**	25
IXb	Nontoxic, 5000	400	0	25
IXc	The same	400	77±8**	25
IXd	Nontoxic, 2000	400	62±10**	24
X	Nontoxic, 1000	300	21±9	20
XIa	The same	300	40±11**	20
XIb	Nontoxic, 1500	500	40±13*	15
XIc	The same	500	20±13	10
XII	1500	500	13±9	15
XIII	Nontoxic, 2000	500	13±9	15
Time of administration 3 h before irradiation				
VIIa	Nontoxic, 2000	500	75±10**	20
V	The same	500	47±13**	15
XII	1500	500	27±11	15
XIII	Nontoxic, 2000	500	27±8	30
Control — males			6±2	190
Control — females			5±4	40

Note. One asterisk means the differences from the control are significant at $P \leq 0.05$, two asterisks at $P < 0.01$; three asterisks indicate that the substances are soluble in water.

For 13 compounds LD_{50} was 300-2000 mg/kg, which is evidence of their moderate and low toxicity. It seemed possible to follow the relationship of the toxic action to the structure of these substances. Derivatives of benzophenone with three methyl groups in both rings (Ih, i) are relatively nontoxic ($LD_{50} \geq 2000$ mg/kg). In the presence of one methoxyl group and one methyl group (If, g), LD_{50} was 550-1100 mg/kg, and in the presence of chlorine

and a methyl group (Ib-d) it was 360-800 mg/kg, depending on the position of the chlorine. Benzophenones Ij-l, in which two to three methyl groups were combined with chlorine, methoxyl, or a nitro group, were equally toxic: LD_{50} 300-620 mg/kg. The presence of chlorine in the molecule evidently was also responsible for a definite toxicity of VI (LD_{50} 340 mg/kg).

The picture of poisoning was characterized by an inhibition of motor activity, ataxia, and a decrease in the reaction to tactile and pain stimuli. For most of the compounds the symptoms of poisoning increased for a period of 15-40 min after their introduction into the organism, for VIIa after 3 h. The mice died with symptoms of cardiac and respiratory insufficiency, sometimes (IVa) against a background of convulsions for 1-2 days.

As can be seen from Table 1, among the substances studied 28 exhibited no radioprotective properties, 10 compounds increased the survival by 30-50%, and four substances increased survival by more than 50%. The latter included fluorenone, myricetin-3'-glucoside, quercetin-7-glucoside, and kaempferol-3,7-dirhamnoside. When administered 15 min before irradiation in doses of 500, 400, 400, and 400 mg/kg, respectively, they provided 53, 60, 77, and 62% survival of the mice, versus 5-6% in the control.

As is well known, a 15 min interval between the administration of the substances and irradiation has been substantiated by the Tactical-Technical Requirements for the Selection of Radioprotectors, but it is evidently acceptable only for substances with emergency action. For 2-benzoylfluorene, with delayed clinical effects of poisoning, this time could scarcely be the only period for testing. As can be seen from Table 1, when 2-benzoylfluorene was administered 3 h before irradiation, 75% of the mice died. Evidently fluorenone also exhibits prolonged action: When it was administered both 15 min and 3 h before irradiation, 47-53% of the animals survived. All the enumerated substances exhibited a protective effect, chiefly in the period of development of the bone marrow syndrome, as judged according to the dynamics of the death of the experimental and control mice.

On the basis of the data presented, we can consider it justified to search for active substances in the series of ketones. A protective effect is exhibited by ketones, in the molecule of which the carbonyl group is conjugated with the aromatic ring, activated by electron donor groups (hydroxyl or a second ring). The radioprotective effect of these substances is evidently based on their interaction with metal ions and metal-containing enzymes, which may promote a stabilization of the redox processes in the cells of the critical organ. Conjugation with the π-electrons of one ring is insufficient: All the benzophenone derivatives of dibenzyl, diphenylmethane, and diphenylethane, in which the two rings are separated by methylene groups, which interrupt the conjugation, are inactive. At the same time, among certain benzoyl derivatives of diphenyl, fluorene, dibenzothiophene, as well as in flavonoids, fluorenone, and 2-methyl-5-hydroxyindanone, which have conjugation of two aromatic rings or an aromatic ring with strong electron donor substituents with the carbonyl, moderate or significant activity was detected. For the same reason, 2-substituted acyl derivatives, in view of the steric hindrance created by a substituent in the ortho-position, are less active in comparison with meta- and para-derivatives: IIc and IIb, IId and IIe, XIc and XIa-b. In quercetin-3-glucoside, the hydroxymethylene substituent in the carbohydrate portion of the molecule also prevents conjugation of the dihydroxyphenyl group with the carbonyl. The influence of the carbonyl on the radioprotective properties in indicated by the results of testing of fluorene and 2-benzylfluorene: the latter are inactive, in contrast to fluorene and 2-benzoylfluorene.

Thus, in the process of screening for radioprotective activity, among 42 substances studied for the first time, five compounds were discovered that promote 53-77% survival of mice at the minimum absolutely lethal dose of irradiation: quercetin-7-glucoside, myricetin-3'-glucoside, kaempferol-3,7-dirhamnoside, and fluorenone, in doses of 400, 400, 400, and 500 mg/kg, respectively, when administered 15 min before irradiation, and 2-benzoylfluorene in a dose of 500 mg/kg administered 3 h before irradiation. A further search for radioprotectors in the series of flavonol glycosides and ketoderivatives of fluorene is advisable.

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THE EFFECTS OF THE AMINO GROUP AND THE HETEROATOM ON THE ANTICONVULSANT ACTIVITY OF 2-SUBSTITUTED 3-AMINO-6,6-DIMETHYL-5,6-DIHYDRO-8H-PYRANO [THIOPYRANO][4',3':4,5]THIENO[2,3-d]PYRIMIDINE-4-ONES

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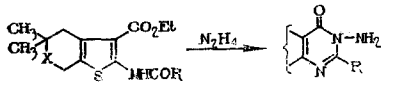
UDC 547.735:854.615.786

In earlier work we showed that 4,5-condensed 2-aminosubstituted 3-carbethoxythiophenes, 4-alkyl(aryl)aminosubstituted thieno[2,3-d]pyrimidines and 2-alkyl substituted thieno[2,3-d]pyrimidinones exhibited anticorazole properties [1-3]. It was noted that the anticonvulsant activity was influenced by the character and position of the substituent in the pyrimidine ring, and also by the nature of the heteratom [4].

In order to investigate further the effects of the amino group at position 3 of the pyrimidine ring and the heteroatom on the anticonvulsant activity, we have prepared 2-alkyl-3-amino-6,6-dimethyl-5,6-dihydro-8H-pyrano(thiopyrano)[4',3':4,5]thieno[2,3-d]pyrimidine-4-ones (XIV-XXVI) by the action of N_2H_4 on substituted 2-amino-3-carbethoxythiophenes I-XIII [1, 2].



I-XIII XIV-XXVI

I, XIV: X = O, R = Me; II, XV: X = O, R = Et; III, XVI: X = O, R = Pr; IV, XVII: X = O, R = *i* = Pr; V, XVIII: X = O, R = Bu; VI, XIX: X = O, R = *i* = Bu; VII, XX: X = O, R = C_5H_{11}; VIII, XXI: X = O, R = C_9H_{10}; IX, XXII: X = O, R = $C_6H_4OBu = i\text{-}n$; X, XXIII: X = S, R = Pr; XI, XXIV: X = S, R = *i* = Pr; XII, XXV: X = S, R = Bu; XIII, XXVI: X = S, R = C_5H_{11}.

A. L. Mndzhoyan Institute of Fine Organic Chemistry, Academy of Sciences of the Armenian SSR, Erevan. Translated from Khimiko-farmatsevticheskii Zhurnal, Vol. 19, No. 5, pp. 557-560, May, 1985. Original article submitted June 12, 1984.

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