EXPERIMENTAL METHOD

Hydrazones of 5(6)-Benzimidazolylhydrazine (I-XIII). A solution of 2.22 g (0.01 mole) of 5(6)-hydrazinobenzimidazole dihydrochloride in 5-10 ml of water is treated with an equimolar amount of the appropriate carbonyl compound, and heated on a water bath for 10-30 min, until the hydrazone-formation reaction is complete. As it is formed, the hydrazone may precipitate from the hot reaction mixture, as in the case of the hydroxybenzaldehydes and pyruvic acid, or it may remain in solution. At the end of the reaction, alcohol (50-100 ml) is added until the boiling solution is saturated. After cooling the latter, the product is precipitated by adding 5-10 ml of concentrated hydrochloric acid. The precipitate is filtered off, washed with alcohol (10-15 ml), and recrystallized from aqueous alcohol (75-150 ml) in the presence of activated charcoal. After cooling the filtrate, concentrated hydrochloric acid (5-30 ml) and ether (10-15 ml) are added for more complete separation of the product. The precipitate is filtered off, washed with alcohol, and dried in vacuo over calcium oxide and calcium chloride.

Hydrazones of 5-Benzotriazolylhydrazine (XIV-XIX). A solution of 2.3 g (0.01 mole) of 1-(2-hydroxyethyl)-5-hydrazinobenzotriazole hydrochloride in 10-15 ml of water is treated with a solution of an equimolar amount of the appropriate carbonyl compound in 10 ml of alcohol. The reaction mixture is heated for 10-40 min until the hydrazone is formed. The precipitate formed on cooling the reaction mixture is recrystallized from 50-150 ml of alcohol containing activated charcoal.

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NEW ANALOGS AND HOMOLOGS OF METHINDIONE

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UDC 615.213:547.665

The amino derivatives of 1,3-indanedione constitute a new class of spasmolytic compounds [1-4]. The most promising agent for the treatment of epilepsy has been found to be the hydrochloride of 2-methylamino-2-ethyl-1,3-indanedione (IIa), which has been authorized for medical use under the provisional name methindione. To judge by the results obtained, this compound is almost ideal in its properties as a spasmolytic agent and is considerably more effective than the preparations that have been used hitherto for the treatment of epilepsy. The main advantages of methindione lie in its high efficacy in cases of general tonic-clonic spasms, its rapid intervention in the status epilepticus, and its normalizing effect on the psyche of the patient.

With the object of increasing the overall methindione yield and simplifying the technological process, we have developed a new method of synthesizing methindione which is more efficient and simpler than the known methods [4-6]. In this new method, the reaction between 2-bromo-2-ethyl-1,3-indanedione (I) and methylamine is carried out in benzene in the presence of dimethylformamide or dimethyl sulfoxide in a volume ratio of 1 : 0.2-0.4. Owing to their catalytic properties, the addition of these strongly polar aprotic solvents accelerates the nucleophilic substitution of bromine by methylamino, with the result that the share of competing side reactions is reduced and the yield of IIa is increased.

The byproducts formed in the reaction between I and methylamine are 2,2'-diethylbis-1,3-indanedione (III) and 2-ethyl-1,3-indanedione. It is clear that in this case the bromine atom has a tendency to enter

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Translated from Khimiko-Farmatsevticheskii Zhurnal, Vol. 10, No. 2, pp. 63-68, February, 1976. Original article submitted July 12, 1974.

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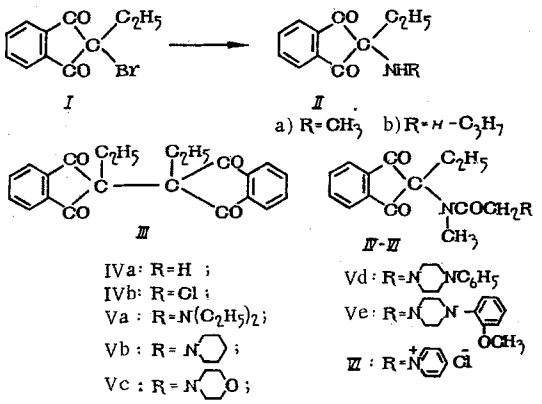
TABLE 1. Pharmacological Activity of Methindione Homologs and Analogs

Compound	LD_{50} (mg/kg)	ED_{50} (mg/kg)						Hexenal narcosis potentiation index
		revolving rod	"tube" test	hypothermia	analgesia	electric shock spasms	corazole spasms	
IIa	600 (540÷739)	215 (177÷244)	230 (184÷283)	115 (89÷150)	80 (67÷96)	45 (39÷52)	28 (23÷34)	1,8
IIb	950 (819÷1102)	50 (33÷75)	50 (33÷75)	145 (127÷165)	200	130 (109÷155)	100	2,54
IVa	28 (22÷35)	—	—	—	—	—	—	—
IVb	700 (625÷782)	260 (168÷315)	260 (168÷315)	175 (113÷238)	200	—	—	0,82
Va	700 (625÷782)	93 (78÷111)	93 (78÷111)	165 (127÷215)	145 (127÷165)	155 (116÷208)	80 (59÷109)	2,57
Vb	440 (411÷471)	93 (78÷111)	93 (78÷111)	70 (37÷133)	72 (55÷95)	95 (82÷120)	98 (67÷142)	2,93
Vc	980 (675÷1421)	93 (78÷111)	93 (78÷111)	45 (24÷86)	165 (127÷214)	300 (252÷354)	200 (133÷300)	2,77
Vd	1650 (1269÷2145)	41 (27÷66)	41 (27÷66)	245 (215÷269)	500	350 (269÷455)	200	8,04
VI	107 (95÷120)	27 (17÷43)	27 (17÷43)	—	—	—	—	0,43

reactions characteristic of positively polarized halides [7-9], i.e., oxidation takes place with intermediate formation of a 2-ethyl-1,3-indanedione free radical, or electrophilic substitution of the halogen by hydrogen occurs.

In [3], 2-amino derivatives of 2-ethyl-1,3-indanedione are described. In the present work, we will describe a method of synthesizing yet another homolog of methindione, viz., 2-n-propylamino-2-ethyl-1,3-indanedione, and evaluate its pharmacological properties.



The salts of 2-methylamino-2-ethyl-1,3-indanedione with several organic acids were prepared in [4]. For the purpose of a comparative pharmacological study, we have synthesized salts of IIa with other organic acids. Methindione base (IIa) forms salts with salicylic and p-toluenesulfonic acid, but not with benzoic, malonic and naphthalic acid.

The reaction of methindione (IIa) with acid chlorides gives N-acyl derivatives (IVa, IVb). When heated in dimethylformamide solution with secondary amines, the chloroacetyl derivative (IVb) forms 2-(N-aminoacetyl-N-methylamino)-2-ethyl-1,3-indanediones (Va-e). With pyridine, the salt product VI is obtained. Compounds of this type have also been studied amongst the amino derivatives of 2-methyl-1,3-indanedione [10].

The experimental study of the 2-amino and 2-aminoacetyl derivatives of 2-ethyl-1,3-indanedione was carried out in experiments on white mice, in which the test substances were injected intraperitoneally.

The following were studied: acute toxicity; spasmolytic activity, using the maximum electric shock test [11] and on the basis of the neutralization of the spasmogenic action of corazole; disturbance of movement coordination and muscle tone by means of the revolving rod method [12] and the "tube" test [13]; and hypothermic action, determined as the mean effective dose required to lower the body temperature of the animals by 3° or more. The analgetic action of the substances was studied by the hot-plate method [14].

The results obtained were processed statistically, the mean effective doses (ED_{50}) and mean lethal doses (LD_{50}) being calculated by the method of Litchfield and Wilcoxon [15]. In addition, we determined

the hexenal narcosis potentiation index, i.e., the ratio of the duration of narcosis in the test animals to the duration of narcosis in control animals. The experimental data are given in Table 1.

It follows from the data given that all the 2-amino- (IIa, IIb) and 2-(N-aminoacetyl-N-methylamino)-2-ethyl-1,3-indanediones (Va-e) studied display spasmolytic properties in the maximum electric shock test and the corazole spasm test, while 2-(N-acetyl-N-methylamino)-2-ethyl-1,3-indanedione and its chloro derivative, and also the pyridinium salt (VI), do not possess spasmolytic activity. All the substances studied are considerably inferior to methindione (IIa) in their spasmolytic activity.

The substances studied exhibit some tranquilizing properties, i.e., they disturb the coordination of movements, lower the body temperature, give an analgetic effect, and potentiate hexenal narcosis. The tranquilizing properties are most marked in the phenylpiperazino derivative (Vd), which has a hexenal narcosis potentiation index of more than 8.

To supplement the investigations carried out, we compared the spasmolytic activity of methindione (the hydrochloride of 2-methylamino-2-ethyl-1,3-indanedione) with that of other salts (maleate, salicylate, tosylate) of this compound. It was found that the salts studied did not differ significantly in their spasmolytic activity or in the duration of their action.

EXPERIMENTAL METHOD

The IR spectra were recorded on a UR-10 instrument using nujol suspensions and a sodium chloride prism. The molecular weights were determined on an MS-905 mass spectrometer.

2-Methylamino-2-ethyl-1,3-indanedione Hydrochloride (IIa · HCl). A benzene solution (600 ml) of bromide I obtained from 148 g (1 mole) of phthalic anhydride [3, 5] was treated, after separating calcium chloride, with 140-200 ml of dimethylformamide or dimethyl sulfoxide and saturated with 31.8 g of dry methylamine at a reaction-medium temperature of about 10°. The flask was sealed and kept at room temperature for 5 h; methylamine hydrobromide precipitated and the reaction mixture became dark-red. The mixture was washed with water (3 × 350 ml), and the organic part extracted with dilute (1 : 4) hydrochloric acid (2 × 150 ml). The acid extracts were combined and adjusted to pH 8.0-9.0 by the slow addition of about 65 ml of 25% aqueous ammonia while cooling with ice water. The precipitate was separated after 3 h and washed with water to give 40 g of a yellow substance with a mp of 106° (from ethanol). This substance was dissolved in 350 ml of benzene and the hydrochloride precipitated by introducing hydrogen chloride. The precipitate was separated after 2 h to give 41 g (17.1% of theoretical yield based on phthalic anhydride) of a white crystalline substance, with a mp of 225-227° (decomp.) after recrystallization from absolute ethanol. Found (%): C 60.24; H 5.81; Cl 14.94; N 5.89. $C_{12}H_{13}NO_2 \cdot HCl$. Calculated (%): C 60.13; H 5.88; Cl 14.80; N 5.84.

The red wash waters were acidified with dilute hydrochloric acid. An oil separated and solidified after cooling to 0°. This was separated and crystallized from ethanol to give about 4 g of 2-ethyl-1,3-indanedione with a mp of 51-53° (a mixed sample with authentic 2-ethyl-1,3-indanedione did not give melting point depression).

The benzene layer remaining after separation of the acid extract was washed with water, dried with calcium chloride, and the solvent evaporated off in vacuo. The residue was crystallized from ethanol to give about 5 g of III, mp 226° (from ethanol). This was insoluble in water, hydrochloric acid and aqueous alkali. Found (%): C 76.81; H 5.55. $C_{22}H_{18}O_4$. Calculated (%): C 76.26; H 5.24. Molecular weight 346 (calculated 346). Infrared spectrum: $\nu_{C=C_{arom}}$ 1585 cm^{-1}; $\nu_{C=O}$ 1696 and 1733 cm^{-1}.

2-n-Propylamino-2-ethyl-1,3-indanedione (IIb). A solution of 3.5 g (0.06 mole) of n-propylamine in a mixture of 30 ml of benzene and 15 ml of dimethylformamide was added at room temperature to a solution of 7.6 g (0.03 mole) of bromide I in 20 ml of benzene. The mixture was worked up similarly to the previous experiment to give 2.3 g (33.3%) of yellow IIb, mp 97° (from ethanol). Found (%): N 6.25. $C_{14}H_{17}NO_2$. Calculated (%): N 6.06. Infrared spectrum: $\nu_{C=C_{arom}}$ 1590 cm^{-1}; $\nu_{C=O}$ 1710 and 1745 cm^{-1}.

Hydrochloride (IIb · HCl). A solution of the base IIb in ether was saturated with hydrogen chloride, and the precipitated salt separated and crystallized from absolute ethanol with addition of ether, mp 229-231° (decomp.); soluble in water. Found (%): C 62.83; H 6.87; Cl 13.43; N 5.20. $C_{14}H_{17}NO_2 \cdot HCl$. Calculated (%): C 62.81; H 6.78; Cl 13.24; N 5.23. Infrared spectrum: $\nu_{C=C_{arom}}$ 1595 cm^{-1}; $\nu_{C=O}$ 1715 and 1755 cm^{-1}.

2-Methylamino-2-ethyl-1,3-indanedione Salicylate. A solution of 1.38 g (0.01 mole) of salicylic acid in ethanol was added to a solution of 2.03 g (0.01 mole) of IIa in benzene. After 5-6 h, the salt precipitat-

TABLE 2. Aminoacetyl Derivatives of Methindione

Compound	Yield (%)	Melting point (deg)	Found (%)				Empirical formula	Calculated (%)				IR spectrum, ν, cm^{-1}	
			C	H	Cl	N		C	H	Cl	N	$C=C_{arom}$	C=O
Vb	48,5	73	70,05	7,51		8,53	$C_{19}H_{24}N_2O_3$	69,50	7,37	—	8,53	1600	1640, 1715, 1745
Vb·HCl		244—5 (dec.)	61,94	7,04	10,08	7,19	$C_{19}H_{24}N_2O_3 \cdot HCl$	62,55	6,91	9,72	7,68	—	—
Vc	36,5	109	65,70	6,67	—	8,69	$C_{18}H_{22}N_2O_4$	65,45	6,71	—	8,48	1600	1640, 1715, 1745
Vc·HCl		237(dec.)	58,37	6,60	10,19	7,24	$C_{18}H_{22}N_2O_4$	58,93	6,32	9,66	7,64	—	—
Vd	94,0	185	70,63	6,68		10,29	$C_{24}H_{27}N_3O_3$	71,08	6,71		10,36	1600	1636, 1718, 1747
Vd·2HCl		244—6 (dec.)	60,60	6,36	14,51	8,99	$C_{24}H_{27}N_3O_3 \cdot 2HCl$	60,24	6,11	14,82	8,78	—	—
Ve	18,4	98	68,29	6,87	—	10,02	$C_{25}H_{29}N_3O_4$	68,93	6,71		9,65	1600	1645, 1715, 1750

*Compounds Vb, Vc, and Ve were crystallized from ethanol, Vd from dimethylformamide, and their hydrochlorides from absolute ethanol.

ing at 0° was separated to give 2.6 g (76.5%) of the salt, mp 114-115° (from absolute ethanol); soluble in water. Found (%): C 66.57; H 5.50; N 4.06. $C_{19}H_{19}NO_5$. Calculated (%): C 66.85; H 5.62; N 4.10.

2-Methylamino-2-ethyl-1,3-indanedione Tosylate. The salt was prepared analogously to the previous experiment from 2.03 g (0.01 mole) of IIa and 1.72 g (0.01 mole) of p-toluenesulfonic acid, in a yield of 3.7 g (98.6%), mp 180° (from absolute ethanol with addition of ether); soluble in water. Found (%): C 60.81; H 5.59; N 3.66; S 8.41. $C_{19}H_{21}NO_5S$. Calculated (%): C 60.78; H 5.64; N 3.73; S 8.54.

2-(N-Acetyl-N-methylamino)-2-ethyl-1,3-indanedione (IVa). A mixture of 4.8 g (0.02 mole) of IIa·HCl and 5 ml of acetyl chloride in 30 ml of dimethylformamide was heated on a water bath for 1 h. The mixture was poured into 200 ml of water and neutralized with ammonia to precipitate a white substance, mp 122° (from ethanol). Yield 3.6 g (75.5%). Found (%): C 68.66; H 6.21; N 5.94. $C_{14}H_{15}NO_3$. Calculated (%): C 68.57; H 6.17; N 5.71. Infrared spectrum: $\nu_{C=C_{arom}}$ 1595 cm^{-1}; $\nu_{C=O}$ 1641, 1711, and 1745 cm^{-1}.

2-(N-Chloroacetyl-N-methylamino)-2-ethyl-1,3-indanedione (IVb). This was prepared analogously to IVa from 4.8 g (0.02 mole) of IIa·HCl and 5 ml of chloroacetyl chloride. Yield 4.3 g (78.8%), mp 133° (from ethanol). Found (%): C 59.82; H 5.10; Cl 12.77; N 5.02. $C_{14}H_{14}ClO_3$. Calculated (%): C 60.10; H 5.04; Cl 12.68; N 5.01. Infrared spectrum: $\nu_{C=C_{arom}}$ 1592 cm^{-1}; $\nu_{C=O}$ 1660, 1710, and 1747 cm^{-1}.

2-(N-Diethylaminoaeetyl-N-methylamino)-2-ethyl-1,3-indanedione (Va). A mixture of 2.8 g (0.01 mole) of IVb and 1.46 g (0.02 mole) of diethylamine in 30 ml of dimethylformamide was heated on a water bath for 2 h. The mixture was poured into 200 ml of water, and the precipitate filtered off and crystallized from ethanol. Yield 2.4 g (76.0%), mp 102° (from ethanol). Found (%): C 68.20; H 7.71; N 8.67. $C_{18}H_{24}N_2O_3$. Calculated (%): C 68.32; H 7.64; N 8.85. Infrared spectrum: $\nu_{C=C_{arom}}$ 1600 cm^{-1}; $\nu_{C=O}$ 1636, 1719, and 1748 cm^{-1}. The data for the analogously prepared aminoacetyl derivatives Vb-Ve are given in Table 2.

Hydrochloride (Va·HCl). This was prepared by passing hydrogen chloride through a solution of Va in a mixture of ether and benzene, giving a colorless substance with a mp of 102° (from absolute ethanol). The salt decomposes on heating to form the base, and is soluble in water. Found (%): Cl 10.57; N 7.51. $C_{18}H_{25}ClN_2O_3$. Calculated (%): Cl 10.05; N 7.94. The data for the analogously prepared hydrochlorides of the other aminoacetyl derivatives Vb·HCl-Ve·HCl are given in Table 2.

2-(N-Pyridinioacetyl-N-methylamino)-2-ethyl-1,3-indanedione Chloride (VI). Dry pyridine (5 ml) was added to 2.8 g (0.01 mole) of IVb. On the following day, ether was added to precipitate VI in a yield of 2.9 g (80.5%); mp 204-206° (decomp.) after crystallization from absolute ethanol; soluble in water. Found (%): C 63.20; H 5.31; Cl 9.61; N 7.39. $C_{19}H_{19}ClN_2O_3$. Calculated (%): C 63.59; H 5.33; Cl 9.68; N 7.81. Infrared spectrum: $\nu_{C=C_{arom}}$ 1590 and 1605 cm^{-1}, $\nu_{C=O}$ 1662, 1713, and 1746 cm^{-1}.

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ANTIMICROBIAL ACTIVITY OF THE PYRIDINIUM SALTS OF SOME α-HALO CARBONYL COMPOUNDS

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UDC 615.281:547.822.5

It is known that quaternary ammonium salts containing various functional groups in their hydrocarbon radicals possess physiological activity with a broad spectrum of action. The bactericidal and fungicidal properties of several representatives of this broad class of compounds have been studied most [1-9].

It would be of interest to trace the antimicrobial action of salts obtained from pyridine bases and α-halo carbonyl compounds. With this object, we have synthesized a series of compounds of general formula $RCOCH_2^+NC_5H_4R' \cdot X^-$, where various halo ketones and monohaloacetic acid esters and amides were used as the α-halo carbonyl component $RCOCH_2X$.

Reaction of α-halo carbonyl compounds with pyridine and its substituted analogs, as described in [10-12], gives the corresponding pyridinium salts I-XXV in almost quantitative yields (see Table 1). For comparison of the bactericidal action of the salts of quaternary and tertiary nitrogen bases, we also synthesized N-(4-methylphenacyl)piperidine hydrochloride (XXVI). All the compounds obtained are crystalline substances which are soluble in water and alcohol but insoluble in benzene, ether and hexane. Most of them melt with decomposition. The salts formed by pyridine with the α-bromo esters (I-III) are hygroscopic and deliquesce in air. Compounds VI, XX-XXIV and XXVI are here described for the first time.

The antimicrobial activity of the compounds was investigated by serial dilution with respect to Gram-positive and Gram-negative microorganisms (Staphylococ. 209, E. coli M-17, S. typhimurium, S. paratyphi B, Sh. dys. flexneri, Bact. pyocyaneum, S. enteritidis, and Bac. anthracoides). The substances were dissolved in water and alcohol, and then in Hottinger's bouillon (pH 7.2). The activity of the compounds was evaluated on the basis of the minimum effective concentration during 1-day exposure in a thermostat at 37°.

In the investigation of bacterial action, it was found that compounds I-VII, XI, and XII are not active against any of the microorganisms. It is clear that the lack of activity in this case is due to the low molecular weight of the substances.

The introduction of methyl groups into the phenacyl residue of phenacylpyridinium bromide (XIV) appreciably increases the antimicrobial activity of the compounds against all the microorganisms (cf.

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