1,10-Trimethylene-2-butyl-1,2,3,4-tetrahydropyrazino(1,2-a)indoles Ic, Ie, Ig, Ik, and Ip were prepared by interaction of IIa-e (0.01 mole), sodium borohydride (0.058 mole), and butyric acid (15 ml) in dioxane (20 ml) under the conditions described earlier [3].

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SYNTHESIS AND BIOLOGICAL PROPERTIES OF SOME HETEROCYCLIC DERIVATIVES OF GUANIDINE

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Continuing our work on the synthesis and investigation of the biological properties of guanidine derivatives of quinoline and tetrahydroquinoline [1], we have synthesized 1-guanidinomethyl tetrahydroquinoline (I), 6-guanidinomethyltetrahydrocarbazole (II), and 2-guanidinoquinazoline (III), and studied their properties. Compound I was prepared from 4-phenyl-1,2,3,4-tetrahydroquinoline (IV), which in turn was obtained by the reduction of the corresponding 4-phenylquinoline using sodium in n-butyl alcohol. The 4-phenylquinolines were obtained by the cyclization of β-arylaminopropiophenones [2]. The chloroacetyl derivatives V were converted by means of the urotropine complexes to the aminoacetyl derivatives VI and these, on reaction with 3,5-dimethyl-1-guanylpyrazole hydrochloride, gave 1-guanidinoacetyl-4-phenyltetrahydroquinolines (I). The reaction of 1-chloroacetyl-4-phenyl-1,2,3,4-tetrahydroquinoline (Va) with potassium cyanide in aqueous alcohol gave 1-cyanoacetyl-1,2,3,4-tetrahydroquinoline (VII).

6-Guanidinomethyl-1,2,3,4-tetrahydrocarbazole (II) was synthesized from 6-aminomethyl-1,2,3,4-tetrahydrocarbazole and 3,5-dimethyl-1-guanylpyrazole hydrochloride.

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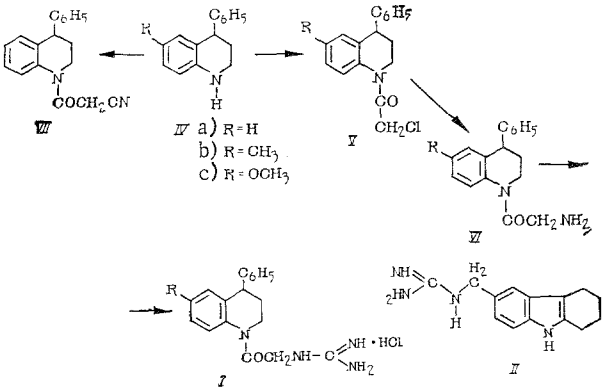
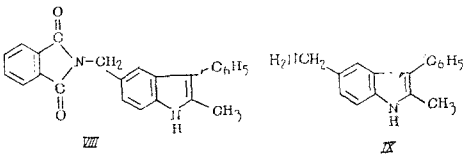
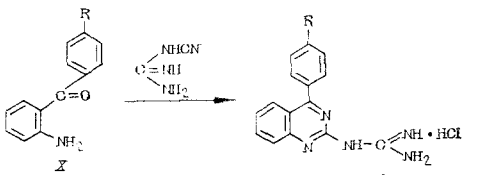


Attempts were made to prepare 5-guanidinomethyl-2-methyl-3-phenylindole in the same way. Amidomethylation of the 2-methyl-3-phenylindole of N-methylolphthalimide in sulfuric acid gave the 5-phthalimidomethyl derivative (VIII) which was hydrolyzed to give 5-aminomethyl-3-phenylindole (IX). However, the guanidine derivative could not be obtained by reaction with 3,5-dimethyl-1-guanylpyrazole hydrochloride; the product of the reaction was an oil which failed to crystallize on long standing.



The reaction of the hydrochloride of o-aminobenzophenone (X) [3] with dicyanodiamide gave 2-guanidinoquinazoline (III).



IIIa: R = CH_3, b: R = OCH_3, c: R = Cl, d: R = Br

The action of compounds IIIa, b, IVc, Va c, VIa, and VII on *Trichomonas vaginalis* was studied *in vitro*. The compound 1-chloroacetyl-4-phenyl-6-methoxy-1,2,3,4-tetrahydroquinoline was found to be active and in concentrations of 0.5-2 μg/ml inhibited the growth of protozoa. The other compounds suppressed the growth of *Trichomonas vaginalis* at concentrations of 250-100 μg/ml.

The tuberculostatic activity of compounds IIIa, c, IVc, Va, c, VIa, and VII against tubercular mycobacteria type $H_{37}Rv$ and atypical mycobacteria type ATCC-607 (compound IIIa) was studied using the method of serial dilution in Soton's medium.

As seen from Table 1, the tetrahydroquinoline derivatives VIa and VII possess weak tuberculostatic activity and compounds IVc and Va, medium activity. Compound Vc-1-chloro-

TABLE 1. Tuberculostatic Activity of Compounds

Compound	Minimum tuberculostatic concn. (type $H_{37}Rv$)		Minimum tuberculostatic activity (type ATSS-607), μg/ml)
	Soton's medium without serum	Soton's medium with serum	
IIIa	0,12	2	0,5
IIIc	3,9	—	—
IVc	7,8	—	—
Va	2	—	—
Vc	1	62,5	—
VIa	15	—	—
VII	1000	—	—

TABLE 2. Properties and Yields of 1-Guanidinoacetyl-1,2,3,4-tetrahydroquinolines (I)

Compound	R	mp, °C	Yield, based on 3,5-dimethyl-1-guanylpyrazole hydrochloride, %	Found, %				Empirical formula	Calc., %			
				C	H	Cl	N		C	H	Cl	N
Ia	H	170,5 (with decomp., from absolute alcohol)	84	62,42	6,34	10,04	16,03	$C_{18}H_{20}N_4 \cdot HCl$	62,69	6,14	10,29	16,25
Ib	CH_3	218—220 (from water)	34	62,71	6,13	—	15,55	$C_{19}H_{22}N_4O \cdot HCl$	63,59	6,46	—	15,61
Ic	CH_3O	212,5—214 (with decomp., from alcohol)	67	60,85	6,04	—	14,74	$C_{19}H_{22}N_4O_2 \cdot HCl$	60,87	6,18	—	14,95

TABLE 3. Properties and Yields of 2-Guanidinoquinazolines (III)

Compound	R	mp, °C	Yield, %	Found, %			Empirical formula	Calc., %		
				C	H	N		C	H	N
IIIa	CH_3	300—301 (from a mixture of concentrated HCl— and abs. alcohol, 1:2)	60	61,30	5,09	22,22	$C_{16}H_{15}N_5 \cdot HCl$	61,24	5,14	22,32
IIIb	OCH_3	275—277 (from CH_3OH)	38,6	58,05	4,91	21,39	$C_{16}H_{15}N_5O \cdot HCl$	58,27	4,89	21,24
IIIc	Cl	296—297 (from 20% HCl)	88 (technical product)	51,13	4,25	19,77	$C_{15}H_{12}ClN_5 \cdot HCl$	51,15	4,29	19,88
IIId	Br	185—189 (from 20% HCl)	82 (technical product)	44,95	3,80	17,50	$C_{15}H_{12}BrN_5 \cdot HCl$	45,21	3,81	17,65

TABLE 4. Properties and Yields of 1-Chloroacetyl-4-phenyl-1,2,3,4-tetrahydroquinolines (V)

Compound	R	mp, °C	Yield, %	Found, %			Empirical formula	Calc., %		
				C	H	Cl		C	H	Cl
Va	H	117–118,5	84,3	71,83	5,59	12,52	$C_{17}H_{16}ClNO$	71,45	5,64	12,41
Vb	CH_3	90–92	68,8	72,60	6,12	11,88	$C_{18}H_{18}ClNO$	72,11	6,05	11,83
Vc	CH_3O	93–95	84	68,48	5,60	11,53	$C_{18}H_{18}ClNO_2$	68,46	5,74	11,23

acetyl-4-phenyl-6-methoxy-1,2,3,4-tetrahydroquinoline was highly active; however, the activity decreased sharply in the presence of serum. The quinoline derivatives studied exhibit high or medium tuberculostatic activity (compounds IIIa and c). The activity of compound IIIa decreases in the presence of serum. The toxicity of IIIa was investigated using white mice weighing 14-15 g; the maximum endurable dose was found to be 1.25 mg per mouse.

A pharmacological study of the sympatholytic properties of compounds Ia-c, II, and IIIa-d was conducted using the method outlined in [1]. Tests on nonnarcotized cats showed that compounds Ia-c and IIIa-d caused no weakening of the third eyelid, i.e., they did not inhibit sympatholytic or ganglio-blocking action in doses of up to 20 mg/kg, administered subcutaneously. However, some toxic effects were noted including locomotor depression, anorexia and, in several cases, vomiting. In tests on cats, compound II weakened the eyelid by 1.6 points (mean of three tests); however, this dose caused the death of the animal within 24 to 30 hours after injection. Lower doses did not cause any relaxation of the eyelid. Guanetidine, which was studied for comparison, when administered subcutaneously at a dose of 20 ml/kg caused complete relaxation of the eyelid — 3 points on a previously established scale [1] and did not have any significant effect on the general condition of the animal. In tests using isolated rat spermiduct, in which the sympathetic nerve ends were electrically stimulated, compounds Ia-c and IIIa-d ($1\cdot10^{-5}$-$3\cdot10^{-5}$ g/ml) decreased the amplitude of contraction by 50%. Compound II displayed the same activity at a concentration of $1\cdot10^{-6}$ and guanetidine at $5.4\cdot10^{-7}$ g/ml.

Thus, of the compounds which were studied, only compound II — 6-guanedinomethyltetrahydroxycarbazole — showed any sympatholytic action, but this compound was less effective than guanetidine. No sympatholytic action was observed for either the 1-guanidinoacetyltetrahydroquinolines(Ia-c) or the 2-guanidinoquinazolines (IIIa-d).

EXPERIMENTAL

1-Guanidinoacetyl-1,2,3,4-tetrahydroquinoline (I). Using a flask protected from atmospheric CO_2, 0.02 moles of the 1-aminoacetyl-1,2,3,4-tetrahydroquinoline (VIa-c) obtained from the recrystallized hydrochloride is dissolved in 50 ml of absolute alcohol. The solution is heated on the water bath and a solution of 2.9 g (0.0166 mole) of 3,5-dimethyl-1-guanylpyrazole hydrochloride added from a dropping funnel. The mixture is refluxed for 40 minutes and, after cooling, the precipitate is filtered off and carefully washed with absolute ether to give Ia-c; the properties of these compounds are given in Table 2.

6-Guanidinomethyl-1,2,3,4-tetrahydrocarbazole (II). A mixture of 3 g (0.015 mole) of 6-aminomethyl-1,2,3,4-tetrahydrocarbazole [4] and 35 ml of absolute alcohol is placed in a flask protected from atmospheric CO_2 and heated to boiling on the water bath. A solution of 2.3 g (0.0132 mole) of 3,5-dimethyl-1-guanylpyrazole hydrochloride in 45 ml of absolute alcohol is added from a dropping funnel and the mixture refluxed for 1.5 hours. The alcohol is removed in vacuum, the oily residue treated with absolute ether and chloroform, and the precipitate obtained filtered off and washed with absolute ether to give 3.5 g of the hydrochloride of 6-guanidinomethyl-1,2,3,4-tetrahydrocarbazole (95.3%) based on the 3,5-dimethyl-1-guanylpyrazole. Found, %: C 60.29; H 7.12; N 19.88; Cl 12.50. $C_{14}H_{18}N_4\cdot HCl$. Calculated, %: C 60.31; H 6.87; N 20.10; Cl 12.72.

2-Guanidinoquinazoline (III). An ethereal solution of HCl is added to a solution of o-aminobenzophenone until the amine is completely saturated, the precipitate filtered off and washed with absolute ether. A mixture of 0.008 mole of the o-aminobenzophenone hydrochloride and 0.74 g (0.0088 mole) of dicyanodiamine is heated at 150-160° for 1 h (compound IIIa, for 2 h), whereupon the mixture first melts and then hardens. The solidified mass is ground in a mortar, washed with water and recrystallized to give IIIa-d (Table 3).

TABLE 5. Properties and Yields of 1-Aminoacetyl-4-phenyl-1,2,3,4-tetrahydroquinolines (VI)

Compound	R	X	mp, °C	Yield, %	Found, %				Empirical formula	Calc., %			
					C	H	Cl	N		C	H	Cl	N
VIa	H	HI	233—235 (with decomp., from isopropyl alcohol)	87,2	52,09	4,67	—	6,93	$C_{17}H_{18}N_2O \cdot HI$	51,79	4,86	—	7,11
VIb	CH_3	$^1/_2\ C_2H_2O_4$	163—165 (from absolute alcohol)	65,2	70,00	6,5	—	8,41	$C_{18}H_{20}N_2O \cdot {}^1/_2\ C_2H_2O_4$	70,13	6,50	—	8,61
VIc	OCH_3	HCl	210—213 (with decomp., in ignition capillary from methanol)	54,5	64,50	6,53	10,76	8,96	$C_{18}H_{20}N_2O_2 \cdot HCl$	64,96	6,36	10,65	8,42

4-Phenyl-6-methyl-1,2,3,4-tetrahydroquinoline (IVb). A solution of 129 g (0.54 mole) of β-(p-tolyl)-ethylphenylketone [9] in 800 ml of n-butyl alcohol and 50 ml of concentrated HCl (d 1.19) is heated on the boiling water bath for 9 h. The butyl alcohol is removed in vacuum, the residue made alkaline with 20% NaOH, and the reaction product extracted with chloroform. The extract is dried over potassium carbonate, evaporated in vacuum, and the residue distilled to give 44.05 g (37.3%) of 4-phenyl-6-methylquinoline, bp 183-5° at 2 mm of Hg.

To a hot solution of 23 g (0.105 mole) 4-phenyl-6-methylquinoline in 1000 ml of n-butyl alcohol is added portionwise 48.5 g (2.10 mole) of metallic sodium and the reaction mixture refluxed until the sodium has completely dissolved. Water (100 ml) is added and the butanol removed by steam distillation and the product extracted from the residue with chloroform. The extract is dried with potassium carbonate and evaporated in vacuum to give 21 g of IVb (89.7% based on 4-phenyl-6-methylquinoline) as a rapidly crystallizing oil with mp 83-5° (from absolute alcohol). Found, %: C 86.66; H 7.60; N 6.12. $C_{16}H_{17}N$. Calculated, %: C 86.05; H 7.67; N 6.27.

4-Phenyl-6-methoxy-1,2,3,4-tetrahydroquinoline (IVc). A solution of 158 g (0.62 mole) of β-(p-methoxyphenyl)aminoethyl phenylketone [9] in 1000 ml of n-butanol and 60 ml of concentrated HCl is heated on the steam bath. The butanol is then evaporated in vacuum, the residue made alkaline with 20% NaOH, and the reaction product extracted with chloroform. The extract is dried over potassium carbonate, evaporated in vacuum, and the residue distilled to give 39.2 g (27%) of 4-phenyl-6-methoxyquinoline bp 192-200° at 2.5 mm of Hg.

The 4-phenyl-6-methoxyquinoline is reduced with 49 g of metallic sodium in 1000 ml of boiling n-butanol, and the reaction worked up as for compound IVb to give 21.26 g of IVc (83.5%, based on the 4-phenyl-6-methodyquinoline) as an oil which crystallizes on standing; bp 183-189° at 1.5 mm of Hg and mp 88-90° (from absolute alcohol). Found, %: C 80.06; H 7.20; N 5.77. $C_{16}H_{17}NO$. Calculated, %: C 80.30; H 7.16; N 5.85.

4-Phenyl-1,2,3,4-tetrahydroquinoline (IVa). Bp 169-170° at 0.4 mm of Hg; mp 71-73° (from 50% alcohol); synthesized from β-phenylaminoethylketone [9] by the same method as IVb and c. The reported value of the mp is 74° [10].

1-Chloroacetyl-4-phenyl-1,2,3,4-tetrahydroquinoline (V). A solution of 1 g of 4-phenyl-1,2,3,4-tetrahydroquinoline (IVa-c) in 10 ml of chloroacetylchloride is refluxed on the water bath for 40 minutes. The excess chloroacetylchloride is removed in vacuum and the residue recrystallized from absolute alcohol to give Va-c (Table 4).

1-Aminoacetyl-4-phenyl-1,2,3,4-tetrahydroquinoline (VIa-c). To a solution of 0.046 mole of urotropin in 150 ml of hot 96% alcohol is added 0.046 mole of NaI and 0.046 mole of 1-chloroacetyl-4-phenyl-1,2,3,4-tetrahydroquinoline (Va-c) and the mixture left at room temperature for 24 h (in the case of VIb, for 3 days). The solution is decanted, 190 ml of methanol and 24 ml of concentrated HCl added to the precipitate of the quaternary salt, the mixture shaken and left at the same temperature for a further 24 h (for VIb, 3 days). The NH_4Cl precipitate is separated, washed with methanol, filtered, and the washings evaporated. The precipitate formed is dissolved in water, made alkaline with NaOH solution and the amine extracted with benzene. The extract is dried over NaOH, and after evaporation of the solvent the amines VIa-c are obtained as crystallizing oils. The hydrochloride of VIc and the oxalate of VIb are obtained by treating ethereal solutions of the base with solutions of HCl and oxalic acid in absolute ether. The hydroiodide of VIa is obtained by evaporating the methanolic solution after separation of the NH_4Cl and recrystallization of the residue from isopropyl alcohol. The properties and yields of compounds VIa-c are given in Table 5.

1-Cyanoacetyl-4-phenyl-1,2,3,4-tetrahydroquinoline (VII). A mixture of 2.25 g (0.0079 mole) of Va, 0.6 g (0.092 mole) of potassium cyanide, and 35 ml of alcohol are heated on the water bath for 2 h. After cooling, 20 ml of water are added and the alcohol removed in vacuum; the reaction product is extracted from the residue with chloroform. The extract is dried, evaporated in vacuum, and the residue recrystallized to give 1.36 g (62%) of VII, with bp 135.5-7°C (from absolute alcohol). Found, %: C 78.30; H 5.59; N 9.84. $C_{18}H_{16}N_2O$. Calculated, %: C 78.23; H 5.84; N 10.14.

5-Phthalimidomethyl-2-methyl-3-phenylindole (VIII). To a solution of 37 g (0.18 mole) of 3-phenylindole [11] in 180 ml of H_2SO_4 is added dropwise during 1 h a solution of 31.8 g (0.18 mole) of N-methylphthalimide in 180 ml of H_2SO_4. After 48 h at room temperature, the mixture is poured onto ice, the precipitate separated, washed with water, and dried. This

material is dissolved in chloroform and the solution chromatographed on Al_2O_3. After evaporation of the solvent, 57 g (87%) of VIII is obtained with mp 189.5-90°C (from a mixture of acetone and hexane). Found, %: C 78.74; H 4.84; N 7.55. $C_{24}H_{19}N_2O_2$. Calculated, %: C 78.45; H 5.20; N 7.65.

5-Aminomethyl-2-methyl-3-phenylindole (IX). A suspension of 36.6 g (0.1 mole) of 5-phthalimidomethyl-2-methyl-3-methylindole in 800 ml of methanol and 16.7 ml of hydrazine hydrate are heated on the water bath until completely dissolved and the solution then refluxed for 3 hours. After cooling, excess dilute HCl (1:1) is added and the precipitate filtered off. The filtrate is evaporated to dryness and the residue made alkaline with ammonium hydroxide. The amine is extracted with ether, the extract dried and evaporated in vacuum to yield 11.5 g (48%) of IX with mp 143-6 (from toluene). Found, %: C 81.59; H 6.98; N 11.91. $C_{16}H_{16}N_2$. Calculated, %: C 81.31; H 6.82; N 11.86.

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DIURETIC ACTIVITY OF 2-SUBSTITUTED DIHYDRO AND TETRAHYDROINDOLES

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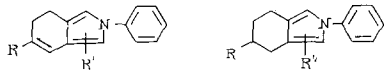
There are reports in the patent literature [1-3] of the high diuretic activity of the isoindoles and their hydrogenated derivatives. Continuing our study of the pharmacological properties of isoindoles [4], we have studied the diuretic activity of some dihydroisoindoles (I-IV) and tetrahydroisoindoles (V-VII):



I-IV

V-VII

I: R, R' = H;
II: R = CH_3, R' = H
III, IV: R = CH_3, R' = CHNNHCONH$_2$

V, VI: R = CH_3, R' = CHNNHC$_6$H$_3$(NO$_2$)$_2$-3
VII: R = H, R' = CHNNHC$_6$H$_3$(NO$_2$)$_2$-3

Compounds I-VII were prepared by the methods given in [4, 5], and their structures were confirmed by UV, IR, and NMR spectra.

EXPERIMENTAL PHARMACOLOGICAL SECTION

The acute toxicity and the diuretic activity of the compounds were studied using three types of animal (mice, rats, and dogs). The acute toxicity was determined on mice in tests

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