SYNTHESIS AND PHARMACOLOGICAL ACTIVITY OF SOME DERIVATIVES OF CONDENSED 1,4-DIHYDROPYRIDINES

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During the past ten years, some 1,4-dihydropyridines have been reported to possess the ability to dilate the coronary vessels of the heart and to relieve ischemia of the heart; one such compound is nifedipine (Adalat) [1-3]. Dihydropyridines are also known to be hypotensive agents [4, 5], and this therefore seemed a promising field in which to look for compounds with cardiovascular activity.

In the present work, the effect on the cardiovascular system and on intestinal smooth muscle of some 1,4-dihydropyridines — derivatives of pyrindenedione (Ia, and b) cyclopentaquinolinetrione (IIa and b), and hexahydroquinoline (IIIa-e) with fused ring systems — has been investigated.

EXPERIMENTAL BIOLOGY

Cats, narcotized with chlorazole (90 mg/kg, intraperitoneally), were used for tests on the systemic arterial pressure; the results were recorded on an electromanometer. Respiration and ECG were recorded.

The ganglion-blocking action of the compounds was studied using the method in which the peripheral vagal stump is stimulated electrically (30 Hz, duration of impulse 0.1 msec, voltage 10 V) for 5 sec every 5 min. Recordings were made on a DMP-4V physiograph ("Narco Bio-Systems").

The effect of the compounds on the smooth muscle of isolated rat intestine treated with acetylcholine (10^{-7} g/ml) and barium chloride (10^{-4} g/ml) was examined. The mean effective concentration (EC_{50}) which decreased the action of acetylcholine and of barium chloride was determined graphically.

The acute toxicity was obtained from tests on noninbred white mice weighing 17-22g; the test preparations were injected intraperitoneally and the mice observed for 7 days. The mean lethal dose (LD_{50}) was calculated by the method of Litchfield and Wilcoxon.

Solutions of the compounds in 50% dimethylacetamide were used for intravenous injections, and suspensions in Tween 80 (5 mg/0.05 ml of a 6% solution) for intraperitoneal injections and for tests on isolated gut.

Of the two derivatives of pyrindinedione with trimethoxyphenyl groups in the 4 position (Ia and b), Ia, which has an ethoxycarbonyl group in the 3 position, showed the greatest hypotensive activity (see Table 1); the mean effective dose of this compound causing a 30% decrease in arterial pressure (ED_{30}) was 1.1 mg/kg. Compound Ia blocked the hypotensive reaction produced by the electrical stimulation of the central fibers of the vagus nerve while at the same time having no effect on the hypotensive action of acetylcholine: this compound also blocked the spasmogenic effect of both acetylcholine and barius chloride on the smooth muscle of the gut.

The cyclopentaquinolinetrione derivatives (IIa [6] and IIb) (0.1-5 mg/kg) had no effect on the systemic arterial pressure or on the frequency of cardiac contractions (see Table 1). Only when the dose was increased to 10 mg/kg was a slight decrease in the arterial pressure and pulse frequency noted. These compounds had no effect on the hypotensive reaction to electrical stimulation of the central fiber of the vagus, i.e., had no effect on the passage of impulses through the parasympathetic ganglia; they blocked the spasmodic effect of barium chloride and to a lesser extent that of acetylcholine.

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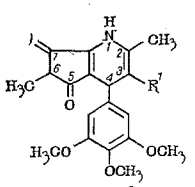
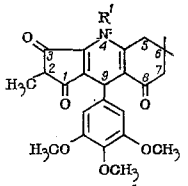
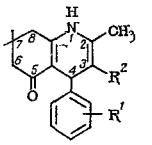
TABLE 1. Pharmacological Activity of Derivatives of Pyrindinedione (I), Cyclopentaquinolinetrione (II), and Hexahydroquinoline (III)



Ia,b



IIa, b



IIIa-e

Compound	R^1	R^2	ED_{50}, mg/kg	ED_{50}, mg/kg (vagal stimulation)	Effect on smooth muscle of the gut: acetylcholine, EC_{50}, g/ml	Effect on smooth muscle of the gut: barium chloride, EC_{50}, g/ml	LD_{50}, mg/kg
Ia	$COOC_2H_5$	—	1,1	5,5	10^{-7}	$1{,}5\cdot10^{-7}$	5000
Ib	$COOC_{12}H_{25}$	—	—	—	$5{,}6\cdot10^{-7}$	$3\cdot10^{-7}$	—
IIa	H	—	—	—	$5\cdot10^{-7}$	10^{-8}	209(167—261)
IIb	CH_2COOH	—	—	—	$2\cdot10^{-7}$	$5\cdot10^{-8}$	1000
IIIa	3=OCH_3	$COOC_2H_5$	—	—	$9\cdot10^{-7}$	$4\cdot10^{-8}$	1000
	4′=OCH_3		—	—	—	—	—
	5′=OCH_3		—	—	—	—	—
IIIb	H(7)	$COOC_2H_5$	—	—	$7\cdot10^{-8}$	$7\cdot10^{-9}$	1000
IIIc	2′=CF_3	$COOC_2H_5$	0,9	1,29	$1{,}7\cdot10^{-7}$	$8\cdot10^{-8}$	100
IIId	H(8)	CN	1,45	3,3	$6{,}5\cdot10^{-8}$	$8\cdot10^{-7}$	—
IIIe	3′=OCH_3	CN	—	—	$2\cdot10^{-7}$	10^{-7}	500
	4′=OCH_3						
	5′=OCH_3						

Of the hexahydroquinoline derivatives, IIIc and IIId, which have a phenyl or trifluorophenyl group in the 4 position, showed the most marked hypotensive action (see Table 1). These compounds also inhibited the development of the hypotensive effect caused by electrical stimulation of the vagus, and blocked the spasmogenic effect of both acetylcholine and barium chloride; compound IIId exhibited mainly a direct myotropic action.

Compound IIIc, which has a trifluoromethylphenyl group, had the highest acute toxicity of all the compounds tested.

These results indicate that some of the derivatives of pyrindinetrione, cyclopentaquinolinetrione, and hexahydroquinoline are active hypotensive agents.

EXPERIMENTAL CHEMISTRY

The Ethyl Ester of 2,6-Dimethyl-4-(3′,4′,5′-trimethoxyphenyl)-5,7-dioxo-1,4,6,7-tetrahydro-5H-1-pyridine-3-carboxylic Acid (Ia). A solution of 5 g (0.0164 mole) of the ethyl ester of β-aminocrotonic acid and 2.14 g (0.0164 mole) of 5-methyl-3-(3′,4′,5′-trimethoxybenzylidene)-cyclopentane-1,2,4-trione in 120 ml of absolute ethanol was refluxed for 3 h. The ethanol was removed, the orange residue dissolved in 10 ml of acetone, transferred to an alumina column, and eluted with ethyl acetate. The first colored fraction was collected and the solvent distilled off, giving 2.8 g (41%) of product, mp 157-158° (from aqueous ethanol) Found, %: C 64.03; H 5.95; N 3.20. $C_{22}H_{25}NO_7$. Calculated, %: C 63.60; H 6.10, N 3.40.

The Dodecyl Ester of 2,6-Dimethyl-4-(3′,4′,5′-trimethoxyphenyl)-5,7-dioxo-1,4,6,7-tetrahydro-5H-1-pyridine-3-carboxylic Acid (Ib) was obtained in the same way as the ethyl ester Ia, from 2 g (0.0065 mole) of the dodecyl ester of β-aminocrotonic acid and 1.77 g (0.0065 mole) of 5-methyl-3-(3′,4′,5′-trimethoxybenzylidene)-cyclopentane-1,2,4-trione. A yield of 1.38 g (38%) of Ib, mp 114-115° (from aqueous ethanol), was obtained. Found, %: C 69.05; H 8.02; N 2.27. $C_{32}H_{45}NO_7$. Calculated, %: C 69.20; H 8.20; N 2.50.

2,6,6-Trimethyl-9-(3′,4′,5′-trimethoxyphenyl)-2,3,4,6,7,9-hexahydro-1H-cyclopenta[6]-quinoline-1,3,8-[5H]trione-4-carboxylic Acid (IIb). A solution of 15.0 g (0.049 mole) of 5-methyl-(3′,4′,5′-trimethoxybenzylidine)-cyclopentane-1,2,4-trione and 9.7 g (0.049 mole) of 3-(N-carboxymethylamino)-5,5-dimethyl-2-cyclohexen-1-one in 200 ml of glacial acetic acid was refluxed for 4 h. The solvent was removed and the bright-yellow residue dissolved in saturated sodium bicarbonate solution. After filtration, the filtrate was neutralized with con-

centrated hydrochloric acid to precipitate the product. A yield of 12.3 g (80%) of IIb with mp 210-215° (with decomposition, from ethyl acetate) was obtained. Found, %: C 64.17; H 5.62; N 2.93. $C_{26}H_{29}NO_8$. Calculated, %: C 64.62; H 6.04; N 2.90.

5-Oxo-2,7,7-trimethyl-4-(3',4',5'-trimethoxyphenyl)-3-ethoxycarbonyl-1,4,5,6,7,8-hexahydroquinoline (IIIa). To a solution of 1 g (0.007 mole) of dimedone in 30 ml of ethanol was added 0.92 g (0.007 mole) of the ethyl ester of β-aminocrotonic acid and 1.4 g (0.007 mole) of 3,4,5-trimethoxybenzaldehyde. The reaction was refluxed for 1.5 h, 20 ml of the solvent removed by distillation, and 30 ml of water added to the remainder. The precipitate obtained was filtered off, given 1.9 g (62%) of white crystals which, after recrystallization from 50% ethanol-dioxane, had mp 217-210°. Found, %: C 66.87; H 7.58; N 3.25. $C_{24}H_{31}NO_6$. Calculated, %: C 67.13; H 7.27; N 3.26.

5-Oxo-2,7,7,trimethyl-4-(o-trifluorophenyl)-3-ethoxycarbonyl-1,4,5,6,7,8-hexahydroquinoline (IIIc). This was obtained in the same way as compound IIIa, from 1 g (0.007 mole) of dimedone, 0.92 g (0.007 mole) of the ethyl ester of β-aminocrotonic acid, and 1.24 g (0.007) mole) of o-trifluoromethylbenzaldehyde by refluxing in 20 ml of ethanol containing 2 drops of triethylamine for 2 h. After distilling off 15 ml of the solvent, the remainder of the reaction mixture was diluted with 20 ml of water and left at 5° for 24 h. Filtration gave 1.65 g (57%) of yellow crystals with mp 178-180° (from 30% ethanol). Found, %: C 63.48; H 5.90; N 3.51; F 14.66. $C_{20}H_{24}NO_3F_3$. Calculated, %: C 63.68; H 6.40; N 3.71; F 15.02.

5-Oxo-2,7,7-trimethyl-4-(3',4',5'-trimethoxyphenyl)-3-cyano-1,4,5,6,7,8-hexahydroquinoline (IIId). To a solution of 2 g (0.0142 mole) of dimedone in 70 ml of ethanol were added 1.18 g (0.0142 mole) of bis-acetonitrile, 2.8 g (0.0142 mole) of 3,4,5-trimethoxybenzaldehyde, and 3 drops of triethylamine. The reaction mixture was refluxed for 3 h, the solvent removed by distillation, and 50 ml of water added, giving 3.7 g (80%) of white crystals mp 237-239° (from 30% ethanol). Found, %: C 68.89; H 6.70; N 7.40. $C_{22}H_{26}N_2O_4$. Calculated, %: C 69.09; H 6.85; N 7.32.

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