the concentration of compound that increased the spasmogenic effect of BK by 100% relative to the original level, was found to be 10^{-6} g/ml for compound III and captopril, and 2×10^{-6} g/ml for compound IV.

The results of these experiments show that compounds III and IV show properties characteristic of ACE (kininase II) inhibitors: the presence of a BK-potentiating effect in vitro and in vivo, diminishment of the pressor reaction of AP on administration of angiotensin-I, and an antihypertensive effect.

Hydrazide IV in experiments in vivo exceeded compound III by a factor of 2 in all biological activities (approaching in several instances that of captopril) that can be associated with the inhibitory influence of the hydrazide group on the process of enzymatic decarboxylation.

The data obtained confirm the possibility of increasing the intensity and duration of effect of inhibitors of ACE that contain carboxyl groups by decreasing the rate of enzymatic decarboxylation, and suggest that the search for compounds of this type that contain mercapto-, carboxyl, and amido groups also include compounds with hydrazide moieties.

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SYNTHESIS AND PHARMACOLOGICAL ACTIVITY OF FURO-1,4-DIHYDROPYRIDINES

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Interest has recently arisen in furo-1,4-dihydropyridines following the detection of good inotropic activity in compounds of this type [3, 9, 12]. Unlike 1,4-dihydropyridines, which are antogonists for calcium ions, furo-1,4-dihydropyridines facilitate the entry of these ions into the cell [4].

Previously reported methods of synthesis of furo-1,4-dihydropyridines [5, 9, 13] are multistage, and require the use of complex reactants. It has recently been shown [6] that pyridinium bromide perbromide reacts with 1,4-dihydropyridines to give furo-1,4-dihydropyridines. We have examined the effects of some other brominating agents on 2,6-dimethyl-3,5-dimethoxycarbonyl-4-(2'-nitrophenyl)-1,4-dihydropyridine (nifedipin, fenigidin) [1]. It was found that these reactions also give furo-1,4-dihydropyridines, and that the best yields were obtained with N-bromosuccinimide (NBS). (See scheme on next page.)

In order to identify new furo-1,4-dihydropyridines with cardiotropic activity, a number of its derivatives were obtained by reacting the 1,4-dihydropyridines (Ia-i) with NBS in chloroform.

The resulting furo-1,4-dihydropyridines (IIa-i) were crystalline solids, stable in the solid state and in solution. Oxidation of (IIb, d, e, g) with 3 N nitric acid gave good yields of the furopyridines (IIIb, d, e, g).

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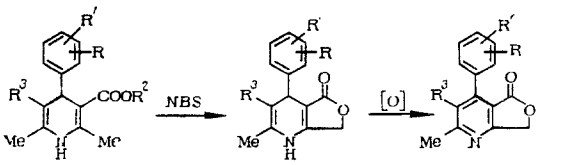
TABLE 1. Maximum Changes in the Strength and Frequency of Spontaneous Contractions of the Isolated Ventricle Induced by the Test Compounds

Compound	Strength of contractions		Frequency of contractions		Species of animal
	concentration, M	change, %	concentration, M	change, %	
IIa	$5{,}8\cdot10^{-7}$	128 ↑	$4{,}6\cdot10^{-7}$	80 ↑	Guinea pigs
IIb	$4{,}1\cdot10^{-7}$	95 ↑	$2{,}0\cdot10^{-7}$	20 ↑	Guinea pigs
IIc	$8{,}0\cdot10^{-7}$	94 ↑	$6{,}5\cdot10^{-7}$	28 ↑	Guinea pigs
IId	$2{,}7\cdot10^{-8}$	44 ↑	$1{,}5\cdot10^{-8}$	0	Rabbits
IIe	$7{,}6\cdot10^{-8}$	107 ↑	$5{,}0\cdot10^{-7}$	6 ↓ /5 ↑	Guinea pigs
IIg	$3{,}0\cdot10^{-8}$	42 ↑	$6{,}0\cdot10^{-8}$	50 ↑	Rabbits
IIh	$9{,}0\cdot10^{-9}$	33 ↑	$8{,}0\cdot10^{-8}$	20 ↑	Guinea pigs
IIi	$4{,}7\cdot10^{-8}$	33 ↑	$1{,}2\cdot10^{-8}$	75 ↑	Rabbits
IIj	$4{,}0\cdot10^{-7}$	51 ↑	$1\cdot10^{-7}$	33 ↑	Guinea
IIIb	$1{,}0\cdot10^{-7}$	17 ↑	$4{,}5\cdot10^{-7}$	0	Rats
IIId	$1{,}2\cdot10^{-7}$	60 ↑	$6{,}0\cdot10^{-8}$	20 ↓	Rabbits



Ia-j IIa-j IIIb,d,e,g

R = 2-$OCHF_2$ (a-d,i), 2-CF_3 (e), 3-CF_3 (f), 3-NO_2 (g), 2-Cl (h), 2-$SCHF_2$ (j);
R^1 = H (a (g, j, 3-NO_2 (h), 4-NO_2 (i);
R^2 = Me (a, d, g, j) Et (b, e, f), Pr-*i* (c);
R^3 = COOMe (a, g-j), COOEt (b, e, f), COOPr-*i* (c), CN (d).

The structures of compounds (II) and (III) were proved by their UV, IR, and PMR spectra.

In general the UV spectra of (II) were similar to those of previously reported furo-1,4-dihydropyridines [1]. In (IIh, i), which have two substituents in the aromatic ring, a fourth absorption maximum was present at around 280 nm. In the oxidized products (III), there was no long wavelength absorption, but a band appeared with a maximum at ~280 nm.

Stretching vibrations of the lactone ring CO group in (II) were seen at 1728-1753 cm^{-1}, and in (III), at 1770-1775 cm^{-1}.

In the PMR spectra of (II), the signals for the protons of the lactone ring methylene group were seen at δ 4.58-4.88 ppm, and in the spectra of (III), the CH_2 protons gave a signal at δ ~ 5.30 ppm.

Pharmacological examination of (II) and (III) was carried out in comparison with the cardiotonic drug strophanthin G, and with the hitherto most active of the furo-1,4-dihydropyridines, CGP 28 392 (IIb) [3]. Their effects on the strength and frequency of spontaneous contractions of the isolated auricle were examined. Most of the compounds, with the exception of (IIIb, d) had good inotropic activity (Tables 1 and 2). The greatest inotropic activity was shown by (IIa), although it was less active than the cardiac glycoside strophanthin G. Compounds (IIb, c, e) also increased the strength of the contractions, but by an order of magnitude less than strophanthin G. The other furo-1,4-dihydropyridines (II) had less effect on the strength of contraction of the auricular musculature. The greatest positive chronotropic activity was shown by (IIa) and (IIc). The furopyridines (IIIb) and (IIId) had negative chronotropic effects. In addition to reducing the strength of the auricular contractions, (IIId) also slightly reduced the frequency of the contractions. Compound (IIIb) had virtually no effect on the frequency of auricular contractions in concentrations up to 10^{-5} M.

Previously reported furo-1,4-pyridines lik wise possessed cardiotonic activity [8] similar to that reported here. The positive inotropic effects of these compounds appear to be mediated by increases in the amounts of calcium entering the cell [4, 11], or to its liberation from a depot within the cell, so that in addition to increasing the contractile capacity of the myocardium, contraction of the vascular smooth muscle is also observed [7, 14].

TABLE 2. Inotropic and Chronotropic Effects of Test Compounds

Compound	Intropic activity	Chronotropic activity
	$EC_{5,0}$, M	
IIa	$(7,8\pm2,0)\cdot10^{-8}$	$4,0\cdot10^{-7}$
IIb	$3,0\cdot10^{-7}$	0
IIc	$2,1\cdot10^{-7}$	$5,0\cdot10^{-8}$
IIe	$5,8\cdot10^{-7}$	0
Strophanthin G	$(3,2\pm0,9)\cdot10^{-8}$	$1,0\cdot00^{-7}$

TABLE 3. Furo-1,4-dihydropyridines (II) and Furopyridines (III)

Compound	Yield, %	mp, °C	Empirical formula	Rf (system)
IIa	58	201—03 [7]	$C_{17}H_{15}F_2NO_5$	0,17
IIb	33	173—05 [7]	$C_{18}H_{17}F_2NO_5$	0,21
IIc	44	160—03 82—88	$C_{19}H_{19}F_2NO_5$	0,36
IId	33	227—030 [7]	$C_{16}H_{12}F_2N_2O_3$	0,08 0,60 [2]
IIe	42	196—08 [4]	$C_{18}H_{16}F_3NO_4$	0,15
IIf	27	194—07	$C_{18}H_{16}F_3NO_4$	0,13
IIg	49	220—03 [9]	$C_{16}H_{14}N_2O_6$	0,20
IIh	55	275—07	$C_{16}H_{13}ClN_2O_6$	0,18
IIi	47	238—040	$C_{17}H_{14}F_2N_2O_7$	0,18
IIj	32	253—07	$C_{17}H_{15}F_2NO_4$	0,14
IIIk	75	109—11	$C_{18}H_{15}F_2NO_5$	0,56
IIIl	74	144—07	$C_{16}H_{10}F_2N_2O_3$	0,60
IIIm	50	127—09	$C_{18}H_{14}F_3NO_4$	0,64
IIIn	80	195—08	$C_{16}H_{12}N_2O_6$	0,64

All the test compounds were of relatively low toxicity with LC_{50} values of greater than 1000 mg/kg (the LD_{50} of strophanthin is 17.5 mg/kg).

The test results show that the greatest cardiotonic activity is displayed by compounds bearing an $OCHF_2$ or CF_3 group in the ortho-position of the aryl substituent, and a carboxyl group in the 3-position [compounds (IIa-e)].

EXPERIMENTAL (CHEMISTRY)

IR spectra were obtained on a Perkin-Elmer instrument (UK), as a Nujol mull, UV spectra on a Specord UV-VIS (East Germany) in ethanol (c $5\cdot10^{-5}$ mole), and PMR spectra on a WH 90/DS (West Germany) (90 MHz) in solution in $CDCl_3$, internal standard tetramethylsilane. The progress of the reactions was followed and the purity of the products checked by TLC on Silufol UV-254 plates in the systems: 1) chloroform–hexane–ethyl acetate (1:1:1), and 2) acetone–hexane (1:1). The elemental analyses were in agreement with the calculated values.

2-Methyl-3-cyano-4-(2'-difluoromethoxyphenyl)-5-oxo-1,4,5,7-tetrahydrofuro[3,4-b]pyridine (IId). A mixture of 1.65 g (0.005 mole) of 2,6-dimethyl-3-cyano-4-(2'-difluoromethoxyphenyl)-5-methoxycarbonyl-1,4-dihydropyridine and 0.89 g (0.005 mole) of NBS in 100 ml of chloroform was stirred for 30 min, then boiled for 30 min. The mixture was then washed with water (2 × 100 ml), 100 ml of hexane added, and the solid which separated filtered off. Crystallization from a mixture of methanol and water (1:1) gave (IId). Obtained similarly were the other furo-1,4-dihydropyridines (Table 3).

2-Methyl-3-ethoxycarbonyl-4-(2'-trifluoromethylphenyl)-5-oxo-5,7-dihydrofuro[3,4-b]pyridine (IIIe). A mixture of 0.37 g (0.001 mole) of (IIe) and 1.75 ml of 3 N nitric acid was stirred for one hour at 70-80°C. Water (50 ml) was then added, and the mixture filtered. Crystallization from ethanol–water (1:1) gave (IIIe). The remaining furopyridines (III) were obtained similarly (Table 3).

EXPERIMENTAL (PHARMACOLOGY)

The effects of the test compounds were examined on the strength and frequency of the contractions of the isolated, spontaneously contracting auricle from rabbits, guinea pigs, and rats [2]. The rabbits were narcotized with hexobarbitone (80 mg/kg intravenously). The

prepared auricles were placed in a dish (30 ml) of Tirode's solution, and oxygenated with oxygen at 30°C. The auricular contractions were recorded isometrically by means of an F-50 sensor and a Narco Bio-Systems physiograph (USA). The test compounds were dissolved in ethanol at an initial concentration of 10^{-2} M. Subsequent dilution was carried out with Tirode's solution. The effects of the compounds were assessed, starting at a concentration of 10^{-9} M.

Acute toxicities were determined in male white mice weighing 19-23 g, by the intraperitoneal route. Each dose was tested on six mice, which were kept under observation for ten days following dosing. The acute toxicities were calculated by the method of Litchfield and Wilcoxon.

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PREPARATION AND BIOLOGICAL ACTIVITY OF ANDROSTANE 17β-CARBOXYLIC ACIDS

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Some androstanecarboxylic acids are known to be biologically active, with a wide spectrum of action, notably antiinflammatory activity [3, 4].

We have previously synthesized some fluorinated 17β-carboxylic acids, and examined their hormonal activity [1].

We have now examined the antiinflammatory activity of some 5α-androstane and Δ^4-androstene acids. As in the earlier report [1], these compounds were obtained by the oxidative cleavage of the pregnane side chain in 20-ketosteroids of general formula (I) with atmospheric oxygen in caustic alkali, to give acids of structure (II).

These compounds (II) were examined as their water-soluble sodium salts, which were more convenient to use, and were obtained by treating a solution of the acid in dichloromethane with 10% sodium carbonate solution, followed by filtration of the crystalline salts which separated.

The structures of the products were confirmed by mass spectrometry. The spectra of all the test compounds showed molecular ion peaks of low intensity, in the case of (IIe), vanishingly small ($I_{M^+} < 0.1\%$). Breakdown of the fluorinated compounds under electron impact re-

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