SYNTHESIS AND PHARMACOLOGICAL PROPERTIES OF 4-GUANIDINOMETHYL- AND 4-(N'-PHENYLAMIDINO)QUINOLINES

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Compounds containing guanidinoalkyl or amidine groups may display sympatholytic and other pharmacological properties [1, 2]. In continuation of the search for biologically active quinolines and tetrahydroquinolines [3], we have synthesized some 4-quanidinomethylquinolines (I) and related 4-(N'-phenylamidino)quinolines (II), and studied their pharmacological effects.

The synthesis of 4-guanidinomethylquinoline (Ia, R = H) and 4-(N'-phenylamidino)quinoline (IIa and b, R = H) was also of interest to us in view of the fact that 2-guanidinomethylquinoline, synthesized and studied by us previously [3], in the form of various water-soluble salts possessed some sympatholytic properties, although it was less active than the drug octadine. Changes in the structure of this compound could result in an improvement in its biological properties.

The intermediate 4-cyanoquinolines (III) used in the synthesis of (I) and (II) were prepared by two methods: 1) from quinoline and 6-methylquinoline via the corresponding quaternary salts and their addition products with HCN, and 2) from isatin and 5-bromoisatin with acetone or acetophenone via the amides of the substituted 4-quinolinecarboxylic acids. Reduction of the 4-cyanoquinolines to the corresponding 4-aminomethylquinolines (IV) was effected with lithium aluminohydride in ether or tetrahydrofuran (THF). It is noteworthy that we were unable to obtain 4-aminomethylquinoldine (IV, R = CH_3) by reducing 2-methylquinoline-4-carboxamide with lithium aluminohydride in boiling dioxan. Approximately 80% of unreacted starting material was recovered. Synthesis of I from the 4-aminomethylquinolines was accomplished by reaction of (IV) with 3,5-dimethyl-1-guanylpyrazole [4]. Preparation of (II) was carried out by fusing the 4-cyanoquinolines with aniline in the presence of aluminum chloride, as in [5].

EXPERIMENTAL (CHEMICAL)

4-Guanidinomethylquinoline (Ia) and 4-Guanidinomethyl-2-phenylquinoline (Ic). In a flask protected from atmospheric CO_2, 0.0133 mole of freshly distilled 4-aminomethylquinoline or 4-aminomethyl-2-phenylquinoline was dissolved in 10-15 ml of absolute alcohol. The solution was heated on the water bath to 50-70°C, a solution of 2 g (0.0114 mole) of 3,5-dimethyl-1-guanylpyrazole hydrochloride in 5 ml of absolute alcohol was added slowly, and the mixture was heated with stirring for 1 h on the boiling water bath. It was then cooled, and the precipitate washed with absolute ether to give (Ia) and (Ic).

4-Guanidinomethylquinaldine (Ib). A solution of 3.28 g (0.0134 mole) of purified 4-aminomethylquinaldine dihydrochloride in the minimum amount of water was made basic with 40% sodium hydroxide, and extracted three times with chloroform. The extract was dried, and evaporated *in vacuo* to give 2.2 g (0.0128 mole) of 4-aminomethylquinaldine base as an oil which crystallized, and which rapidly acquired a violet coloration in air. The amine was placed in a flask protected from atmospheric CO_2, dissolved in 50 ml of isopropanol, heated to 50-70°C , and a solution of 1.67 g (0.0096 mole) of 3,5-dimethyl-1-guanylpyrazole hydrochloride in 20 ml of isopropanol was added slowly. The mixture was heated on the boiling water bath for 2 h, cooled, and the precipitate washed with ether to give 2.16 g of (Ib).

4-(N'-Phenylamidino)quinolines (IIa-f). A mixture of 0.04 mole of (III) and 0.06 mole of aniline was heated to 150°C. Aluminum chloride (0.025 mole) was added portionwise with stirring, and the temperature raised to 185°C and maintained for 10 min. The reaction mix-

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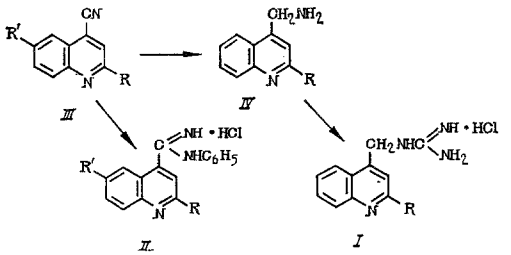

ture, which solidified on cooling, was dissolved in concentrated hydrochloric acid, and the solution poured into water, washed with ether, and made basic. The precipitate was filtered off and dried to give (IIa, c, and e). The dihydrochlorides of (IIb and d) were obtained by adding ethereal hydrogen chloride to solutions of the analytically pure bases in absolute chloroform and acetone, respectively. The dihydrochloride of (IIf) was obtained by adding ethereal hydrogen chloride to an ether solution of the base, and recrystallized from a mixture of concentrated hydrochloric acid and absolute alcohol. Some physicochemical properties of (I and II) are given in Table 1.

4-Cyano-6-methylquinoline (III, R = H, R' = CH_3). To a solution of 90.13 g (0.63 mole) of 6-methylquinoline in 100 ml of benzene was gradually added 79.3 g (0.63 mole) of dimethyl sulfate, and the mixture was heated on the water bath for 1 h. After cooling, 200 ml of water was added and the aqueous layer separated. Ether (100 ml) was added, followed with vigorous stirring by a solution of 34 g (0.693 mole) of sodium cyanide in 150 ml of water from a dropping funnel. The ether layer was separated and cooled in ice-salt. The precipitate was filtered off, washed with water and cold ether to give 73 g of 1,6-dimethyl-4-cyano-1,4-dihydroquinoline which was unstable on keeping. This material (71.2 g, 0.388 mole) was dissolved in 180 ml of pyridine, added to a solution of 98.5 g (0.388 mole) of iodine in 990 ml of alcohol, and stirred at 20°C for 2 h. On cooling with ice-salt, 100 g of 1,6-dimethyl-4-cyanoquinolinium iodide was obtained, mp 205-207°C. This product (60 g, 0.193 mole) was suspended in 120 ml of ethyl benzoate and heated to 210-220°C, collecting the methyl iodide which was given off. The residue was steam-distilled. Ethyl benzoate distilled first, followed by 4-cyano-6-methylquinoline, which crystallized immediately. Yield 22.1 g (36% based on 6-methylquinoline), mp 119-121°C. Found, %: C 78.70; H 4.60; N 16.48. $C_{11}H_8N_2$. Calculated, %: C 78.55; H 4.79; N 16.66.

6-Bromo-4-cyanoquinaldine (III, R = CH_3; R' = Br). 6-Bromoquinaldine-4-carboxamide (16.7 g, 0.063 mole) was suspended in 45 ml of pyridine, and 5.8 ml (0.063 mole) of phosphoryl chloride was added gradually from a dropping funnel, heat being evolved. When the addition was complete, the mixture was heated at the boil for a further 30 min. The solution was cooled and poured into 100 ml of water to give 12 g (77.3%) of 6-bromo-4-cyanoquinoline, mp 158-161.5°C (from ethyl acetate). Found, %: C 53.18; H 3.02; N 11.27. $C_{11}H_7BrN_2$. Calculated, %: C 53.46; H 2.85; N 11.34.

4-Aminomethylquinoline (IV, R = H). Lithium aluminohydride (2.96 g, 0.078 mole) was suspended in 100 ml of absolute ether, the flask purged with nitrogen, and a solution of 6.15 g (0.04 mole) of 4-cyanoquinoline [6] in 400 ml of absolute ether was added from a dropping funnel. The mixture was boiled for 3 h, cooled, and cautiously decomposed with water (14 ml) and 40% sodium hydroxide (23 ml). The ether layer was decanted off, and the residue washed with ether. The combined ether solutions were dried and evaporated *in vacuo*. The residual oil was distilled to give 1.26 g (20%) of IV, bp 151-152°C (2 mm). The dihydrochloride was obtained by adding concentrated hydrochloric aid to an alcoholic solution of the base, and had an mp 250°C (with decomp., from a mixture of concentrated hydrochloric acid and alcohol (2:3). Literature values, 250°C (with decomposition) [7]; 255°C [8].

4-Aminomethylquinaldine (IV, R = CH_3). To a suspension of 3.32 g (0.0875 mole) of lithium aluminohydride in 200 ml of absolute ether was added gradually a solution of 14.7 g (0.0875 mole) of 4-cyanoquinaldine [5] in 500 ml of absolute ether. The reaction mixture was boiled for 6 h, cooled, and decomposed with water (25 ml) and 40% sodium hydroxide (33 ml). The ether layer was decanted, dried, and an ethereal solution of hydrogen chloride added to give 13.4 g (62.5%) of (IV) dihydrochloride, mp 294°C (with decomp., from a 3:2 mixture of absolute alcohol and concentrated hydrochloric acid). Found, %: C 53.64; H 6.07; Cl 29.11. $C_{11}H_{12}N_2 \cdot 2HCl$. Calculated, %: C 53.89; H 5.76; Cl 28.93.

4-Aminomethyl-2-phenylquinoline (IV, R = C_6H_5). To a suspension of 1.33 g (0.035 mole) of lithium aluminohydride in 50 ml of absolute THF was added over 1 h a solution of 8 g

TABLE 1. 4-Guanidinomethylquinolines (I) and 4-(N'Phenylamidino)quinolines (II)

Compound	R	R'	X	mp, °C (solvent for crystallization)	Yield, % (calculated on 3,5-dimethyl-1-guanylpyrazole hydrochloride)	Found, %				Molecular formula	Calculated, %			
						C	H	Cl	N		C	H	Cl	N
Ia	H			228 (with decomp., from methanol–ether)	50,5	55,40	5,85	14,51	23,49	$C_{11}H_{12}N_4 \cdot HCl$	55,81	5,54	14,98	23,67
I	CH_3			218,5—223 (from water)	89,9	57,73	6,19	14,01	—	$C_{12}H_{14}N_4 \cdot HCl$	57,48	6,03	14,14	—
I	C_6H_5			120—122 (with decomp., from absolute alcohol)	55	65,30	5,42	—	17,56	$C_{17}H_{15}N_4 \cdot HCl$	65,27	5,48	—	17,91
IIa	H	H	—	211,5—212,5 (from isopropanol)	62,5	77,86	5,13	—	16,94	$C_{16}H_{13}N_3$	77,71	5,30	—	16,99
II	H	H	2HCl	255 (with decomp.)	—	—		22,22		$C_{16}H_{13}N_3 \cdot 2HCl$	—	—	22,14	—
II	H	CH_3	—	218—220 (from benzene)	93	78,33	5,80	—	15,79	$C_{17}H_{15}N_3$	78,13	5,79	—	16,08
II	H	CH_3	2HCl	263—265 (with decomp.)	—	61,14	5,37	20,51	12,29	$C_{17}H_{15}N_3 \cdot 2HCl$	61,09	5,13	21,21	12,57
II	CH_3	Br	—	204—206 (from benzene)	62,5	60,27	4,55	—	—	$C_{17}H_{14}BrN_3$	60,01	4,15	—	—
II	CH_3	Br	2HCl	251—253 (with decomp.)	—	49,50	3,90	16,80	—	$C_{17}H_{14}BrN_3 \cdot 2CHl$	49,42	3,90	17,16	—

(0.0348 mole) of 2-phenyl-4-cyanoquinoline [5] in 70 ml of absolute THF. The reaction mixture was boiled for 3 h, cooled in ice, water and dilute hydrochloric acid were added cautiously until an acid reaction was obtained. The THF was distilled off *in vacuo*, the aqueous layer shaken several times with benzene to remove neutral impurities, and made basic with sodium hydroxide followed by extraction of the amine with ether. The extract was dried over sodium hydroxide and evaporated *in vacuo* to give 5.3 g (65.4%) of 4-aminomethyl-2-phenylquinoline as an oil, bp 200-210°C (0.3 mm, in a stream of nitrogen). The dihydrochloride was obtained by adding ethereal hydrogen chloride to a solution of the base in absolute ether, mp 250-253°C (with decomp., from an 8:2 mixture of absolute alcohol and concentrated hydrochloric acid). Found, %: C 61.73; H 5.57. $C_{16}H_{14}N_2 \cdot 2HCl$. Calculated, %: C 62.55; H 5.25.

6-Bromoquinaldine-4-carboxamide. A mixture of 50 g (0.22 mole) of 5-bromoisatin, 47.4 g (0.815 mole) of acetone, and 150 ml of 30% aqueous ammonia was heated at 65°C for 3.5 h with stirring, as in [9]. After cooling, the precipitate was filtered off and washed with water to give 57 g (97%) of technical product, from which after repeated recrystallization from acetic acid was obtained 6-bromoquinoldine-4-carboxamide, mp 301-303°C. Found, %: C 49.45; H 3.32. $C_{11}H_9BrN_2O$. Calculated, %: C 49.83; H 3.42.

EXPERIMENTAL (PHARMACOLOGICAL)

The compounds were examined for their effects on the adrenergic endings and other elements of the autonomic nervous system.

The sympatholytic properties and toxicities of the compounds were studied by previously-described methods [3]. Effects on arterial pressure and frequency of cardiac contractions were also studied in urethane-narcotized (1.2 g/kg intraperitoneally) cats.

In non-narcotized cats, (Ia) in a dose of 20 mg/kg subcutaneously caused a slight weakening (1 point) of the third eyelid which lasted for approximately 24 h, but in smaller doses it was inactive. In a dose of 20 mg/kg, guanethidine, for comparison, weakened to the maximum extent (3 points) the third eyelid for 5 days without visible toxic signs. Compounds (Ib, Ic, IIb, IId) and (IIf) in a dose of 20 mg/kg were inactive in this test, and induced repeated vomiting, dyspnea, tremor, and other toxic signs in the animals.

In urethane-narcotized cats, (Ia) in a dose of 10 mg/kg within 2-3 h of its intravenous administration reduced by 30-50% the amplitude of the contractions of the third eyelid in response to electrical stimulation of the postganglionic region of the cervical trunk of the sympathetic nerve. Compounds (Ib, Ic, IIb, IId) and (IIf) were inactive in this test. In a dose of 20 mg/kg intravenously, the drugs caused the death of the animals from respiratory arrest. In experiments on isolated vas deferens from the rat, (Ia) was much less active than guanethidine; (Ib, Ic, IIb, IId) and (IIf) were of low activity (Table 2). Compounds (Ia) (1 μg/kg) and (Ib) (5 μg/kg) in narcotized cats reduced the arterial pressure by 50-70 mm Hg, and decreased the frequency of cardiac contractions from 156 ± 19 to 108 ± 12 per minute. The original arterial pressure and cardiac contraction frequency were restored after 2-3 minutes. The hypotension and bradycardia induced by (Ia) and (Ib) were substantially reduced or completely prevented by prior administration of atropine (0.1 mg/kg) or the ganglion-blocking drug imekhin (0.5 mg/kg), or by cutting the vagus nerves. It may be that the hypotension and bradycardia induced by (Ia) and (Ib) are related to an increase in the activity of the vagal

TABLE 2. Pharmacological Activity and Toxicity of Quinoline Derivatives

Compound	Weakening of the third eyelid (in points) of nonnarcotized cats after administration subcutaneously in a dose of 20 mg/kg	Isolated rat vas deferens, ED_{50}, g/ml	Toxicity in white mice, LD_{50}, mg/kg intravenously
Ia	1	$7,1 \cdot 10^{-6}$	32
Ib	0	$3 \cdot 10^{-5}$	18,5
Ic	0	10^{-4}	26
IIb	0	10^{-4}	69
IId	0	$5 \cdot 10^{-5}$	71
IIf	0	$7,3 \cdot 10^{-5}$	62,5
Guanethidine	3	$5,4 \cdot 10^{-7}$	28,5

nerves as a result of the central effects of these drugs. Compounds (Ic, IIb, IId) and (IIf) did not display the effects typical of (Ia) and (Ib). In small doses, they were without significant effects on blood circulation, and in larger doses up to 5-10 mg/kg they caused a temporary reduction in arterial pressure which was apparently due to a ganglion-blocking effect, since during hypotension induced by (Ic, IIb, IId) and (IIf), the hypertensive reaction to cytizine (15 μg/kg) was reduced.

Thus, (Ia) hydrochloride possesses moderate sympatholytic activity, manifested as weakening of the third eyelid in nonnarcotized rats and a reduction in the contraction of the eyelid in response to electrical stimulation of the postganglionic region of the sympathetic nerve in narcotized cats. A sympatholytic effect was also noted in isolated rat vas deferens. The other compounds were inactive as sympatholytics. Hence, 4-guanidinomethylquinoline is inferior in its sympatholytic activity to the previosly investigated 2-guanidinomethylquinoline [3], and the further introduction into the 2-position of the quinoline ring of a methyl (Ib) or phenyl (Ic) substituent, or replacement of the guanidine group by amidine (IIb, IId, IIf), results in the loss of sympatholytic properties. Compounds (Ia) and (Ib) cause a transient drop in arterial pressure and bradycardia, as a result of central stimulation of the vagus nerves.

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SYNTHESIS AND BIOLOGICAL ACTIVITY OF VITAMIN D_5 AND ITS 3β-FLUORO-DERIVATIVE

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Vitamins D_2 and D_3 are used extensively for the treatment and prophylaxis of rickets, but shortages of the raw materials ergosterol and cholesterol prevent the increasing requirements of medicine and agriculture from being fully satisfied. For this reason, the search for new anti-rickets vitamins is currently of great interest.

Vitamin D_5 (Ia) (sitocalciferol) was described in 1936 by Wunderlich [1], who established that its activity was 1/40 that of vitamin D_3. It was later found [2] that its activity was ¾ that of vitamin D_2 in rats. However, vitamin D_5 has received little attention owing to the difficulty of obtaining the starting material for its synthesis, β-sitosterol, which is obtained in small amounts from grape pomace [2, 3].

Methods have recently been developed for the isolation of β-sitosterol from the waste products from sulfate cellulose manufacture [4, 5], which have enabled it to be produced on a multi-ton scale. To determine whether it would be possible to use vitamin D_5 as an antirachitic, we have synthesized it from β-sitosterol by a route similar to that used for vitamin D_3 from cholesterol, and checked its activity in mammals and birds. At the same time,

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