SYNTHESIS AND CALCIUM ANTAGONIST ACTIVITY OF DIALKYL 1,4-DIHYDRO-2,6-DIMETHYL-4-(NITROGENOUS HETEROARYL)-3,5-PYRIDINE DICARBOXYLATES

Pier G. BARALDI, Roberta BUDRIESI, Barbara CACCIARI, Alberto CHIARINI, Laura GARUTI, Giuseppe GIOVANNINETTI, Alberto LEONI and Marinella ROBERTI

Dipartimento di Scienze Farmaceutiche, Università di Bologna, Via Belmeloro 6, 40126 Bologna, Italy

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Dedicated to Dr Miroslav Protiva on the occasion of his 70th birthday.

A new series of 4-(nitrogenous heteroaryl)-1,4-dihydropyridine antagonists *II*—*XVI* were synthesized and screened for inotropic, chronotropic and calcium antagonist properties, in order to evaluate the effect on pharmacological activity of replacement of the 4-aryl group of nifedipine-like drugs by heterocyclic moieties, such as quinoline, indole, carbazole and pyrazole. The most potent bradycardic compounds of the series (*VIII*—*X*, *XII* and *XIII*) elicited weak calcium antagonist activity and were stronger negative inotropic.

The pharmacological profile of the calcium antagonists, as summarized by the WHO classification[1], can explain the great deal of research in this field, especially within the dihydropyridine group, where nifedipine (*I*) is the prototype. In spite of the great number of papers and patents concerning the structural modifications[2-5] of *I*, many possibilities remained still open. In particular, the nature of the 4-substituent of the dihydropyridine ring, usually a substituted phenyl, should deserve, as far as we know, further investigation. Only limited researches appear to have been carried out, concerning replacement of the aforesaid benzene ring by aromatic heterocycles. The encouraging results obtained following this approach can be illustrated by Mesudipine[6] and Isradipine[7]. As a part of our research program in this field, we report the synthesis and the in vitro pharmacological properties of a series of 1,4-dihydropyridines 4-substituted with nitrogenous heterocycles (1*H*-indole, quinoline, 9*H*-carbazole, pyrazole). A further stimulus to this research were the preliminary results concerning 1,4-dihydro-2,6-dimethyl-4-(pyrazolyl)-3,5-pyridine dicarboxylates[8] recently reported by some of us. The new compounds (*II*—*XVI*, see Table I) were tested to examine the inotropic and chronotropic effects on isolated cardiac preparations from guinea-pig hearts and to evaluate the calcium antagonist activity by their ability to decrease the contractions of potassium depolarized guinea-

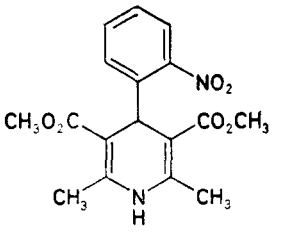
-pig artery strips. The inotropic and chronotropic effects were studied on atrial muscle: left atria driven at 1 Hz and spontaneously beating right atria.

TABLE I

Characterization of compounds *II*–*XVI*

Compound Yield, %	M.p., °C Solvent	Formula (M.w.)	Calculated/Found		
			% C	% H	% N
II	264–265	$C_{19}H_{20}N_2O_4$	67·05	5·92	8·23
45	A–B	(340·4)	67·30	6·00	8·16
III	231–232	$C_{20}H_{20}N_2O_4$	68·17	5·72	7·95
80	A–B	(352·4)	67·95	5·42	7·60
IV	256–257	$C_{25}H_{24}N_4O_6$	63·02	5·08	11·76
56	A–B	(476·5)	62·77	4·68	11·49
V	249–250	$C_{25}H_{26}N_2O_4$	71·75	6·26	6·69
63	C–D	(418·5)	71·30	5·95	6·52
VI	209–210	$C_{20}H_{19}N_3O_6$	60·45	4·82	10·57
53	A–B	(397·4)	60·30	4·82	10·25
VII	310–311	$C_{20}H_{20}N_2O_5$	65·21	5·47	7·60
42	E–F	(368·4)	65·00	5·18	7·38
VIII	223–225	$C_{21}H_{22}N_2O_4$	68·84	6·05	7·65
68	A–B	(366·42)	68·72	5·98	7·54
IX	221–222	$C_{19}H_{26}N_4O_6$	56·15	6·45	13·78
86	A–B	(406·4)	56·06	6·32	13·50
X	134–136	$C_{19}H_{26}N_4O_6$	56·15	6·45	13·78
70	A–B	(406·4)	56·00	6·21	13·47
XI	258–260	$C_{18}H_{24}N_4O_6$	55·09	6·16	14·28
53	A–B	(392·4)	54·95	6·01	14·12
XII	178–179	$C_{18}H_{24}N_4O_6$	55·09	6·16	14·28
55	A–B	(392·4)	54·87	5·98	14·08
XIII	228–229	$C_{17}H_{22}N_4O_6$	53·96	5·86	14·81
58	A–B	(378·4)	53·81	5·79	14·75
XIV	247–249	$C_{17}H_{22}N_4O_6$	53·96	5·86	14·81
65	A–B	(378·4)	53·68	5·76	14·65
XV	239–240	$C_{20}H_{19}N_3O_6$	60·45	4·82	10·57
41	E–C	(397·4)	60·13	4·56	10·45
XIV	248–249	$C_{19}H_{19}N_3O_4$	64·58	5·42	11·89
67	E–F	(353·4)	64·60	5·40	11·75

A ethyl acetate, B petroleum ether (40–60°C), C acetone, D toluene, E chloroform, F methanol



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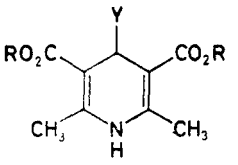
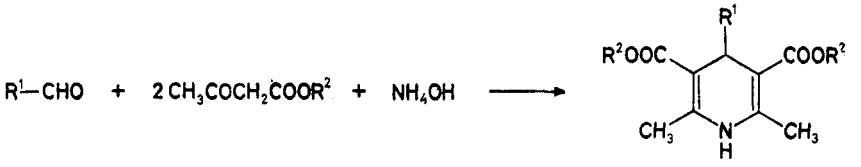


II–XVI

R = CH_3, C_2H_5
Y = nitrogen containing heterocycle

The preparation of the compounds *II*–*XVI* was performed utilizing the classical Hantzsch procedure which involves the simultaneous reaction of an acetoacetate, a nitrogenous heterocyclic carboxaldehyde and ammonium hydroxide in refluxing ethanol or isopropanol (Scheme 1).



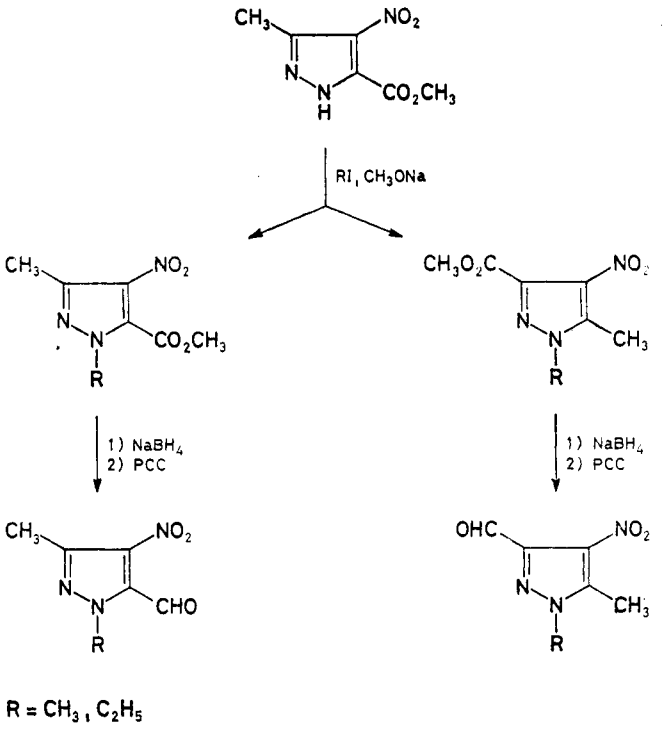
II–XVI

Compound	R^1	R^2
II	indol-2-yl	CH_3
III	quinolin-4-yl	CH_3
IV	6-nitro-3-benzylbenzimidazol-2-yl	CH_3
V	9-ethyl-9*H*-carbazol-2-yl	CH_3
VI	8-nitroquinolin-2-yl	CH_3
VII	2-hydroxyquinolin-4-yl	CH_3
VIII	2-methylquinolin-5-yl	CH_3
IX	1-ethyl-4-nitro-5-methylpyrazol-3-yl	C_2H_5
X	1-ethyl-3-methyl-4-nitropyrazol-5-yl	C_2H_5
XI	1,5-dimethyl-4-nitropyrazol-3-yl	C_2H_5
XII	1,3-dimethyl-4-nitropyrazol-5-yl	C_2H_5
XIII	1-ethyl-3-methyl-4-nitropyrazol-5-yl	CH_3
XIV	1-ethyl-4-nitro-5-methylpyrazol-3-yl	CH_3
XV	8-nitroquinolin-4-yl	CH_3
XVI	quinoxalin-5-yl	CH_3

SCHEME 1

The preparation of pyrazolic carboxaldehydes was performed according to a methodology previously reported[8], starting from methyl (3-methyl-4-nitro-pyrazole--5-carboxylate) through a three-step sequence involving N-alkylation with methyl or ethyl iodide to give 1,3 or 1,5-dialkyl derivatives, followed by reduction with sodium borohydride to the corresponding alcohols and oxidation by means of pyridinium chlorochromate (PCC).

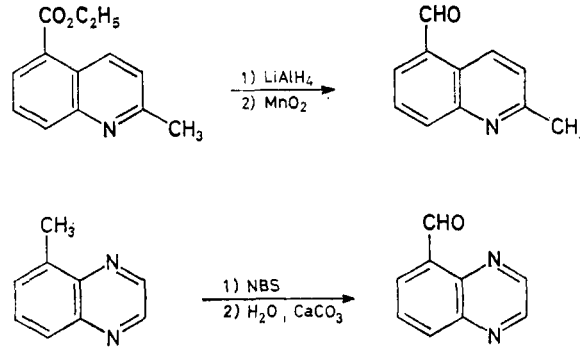
The other heterocyclic carboxaldehydes were commercially available or synthesized according to standard procedures (Scheme 2), with the exception of quinoxaline-5--carboxaldehyde, 2-methylquinoline-5-carboxaldehyde and 2-hydroxyquinoline-4-carboxaldehyde.



SCHEME 2

The latter was obtained by selenium dioxide oxidation of the corresponding methyl derivative in refluxing dioxane containing 4% water according to a reported procedure[9]. The preparation of 2-methylquinoline-5-carboxaldehyde was carried out in good yield from ethyl 2-methylquinoline-5-carboxylate through a two-step sequence involving lithium aluminium hydride reduction to the hydroxymethyl

derivative followed by oxidation with manganese dioxide to the desired compound. Quinoxaline-5-carboxaldehyde was prepared from 5-methylquinoxaline through a different methodology involving N-bromosuccinimide (NBS) bromination followed by hydrolysis in aqueous alcoholic solution in the presence of freshly precipitated calcium carbonate (Scheme 3).



SCHEME 3

The compounds *II*–*XVI* prepared by the general procedure reported in Experimental are assembled in Table I with the usual analytical data and in Table II are collected their proton NMR data.

The pharmacological profile of new DHP compounds (*II*–*XVI*) was assessed on guinea-pig isolated left atria and right atria to evaluate their negative inotropic and/or chronotropic effects and on K^+-depolarized guinea-pig artery strips to test their calcium antagonist activity. All the compounds were first checked at increasing doses to examine the dose-dependent decrease both of the developed tension in the left atria driven at 1 Hz and of the frequency in spontaneously beating right atria, then to measure the inhibitory effect on K^+-evoked contractions in guinea-pig helicoidal aortic strips. For the compounds showing an activity close to that of nifedipine (*I*), used as reference standard, the ED50's, ED30's and IC50's values were evaluated from log concentration–response curves[10] in the appropriate pharmacological preparations.

Table III reports the decrease in the developed tension, the reduction of the beat frequency in atrial preparations and the % inhibition of calcium contraction (80mM-KCl) in vascular smooth muscle (for experimental details see ref.[8]). An inspection of the data reported in Table III shows that the tested compounds are fairly potent as calcium antagonists and some of them exert potent bradycardic effects close to the nifedipine's one. Surprisingly, the most potent bradycardic

TABLE II

^{1}H NMR data for compounds *II*–*XVI*

Compound	Data
II	CD_3SOCD_3: 2·29 s, 6 H (2 Me); 3·62 s, 6 H (2 OMe); 5·1 s, 1 H (C(4)-H); 5·9 s, 1 H (C(3)-H); 6·9 m, 2 H (indole protons); 7·3 m, 2 H (indole protons); 9·0 sb, 1 H (NH-DHP); 10·2 sb, 1 H (NH indole)
III	CD_3SOCD_3: 2·35 s, 6 H (2 Me); 3·44 s, 6 H (2 OMe); 5·85 s, 1 H (C(4)-H); 7·3–7·8 m, 5 H (quinoline protons, NH-DHP); 8·1 d, 1 H (C(2′)-H, J = 8)
IV	CD_3SOCD_3: 2·30 s, 6 H (2 Me); 3·48 s, 6 H (2 OMe); 5·38 s, 1 H (C(4)-H); 5·83 s, 2 H (benzylic protons); 7·07–7·4 m, 6 H (aromatic protons); 8·0 d, 1 H (C(6′)-H, J = 8); 8·49 s, 1 H (C(4′)-H; 9·3 sb, 1 H (NH-DHP)
V	CD_3SOCD_3: 1·25 t, 3 H (CH_3, N-ethyl); 2·34 s, 6 H (2 Me); 3·57 s, 6 H (2 OMe); 4·3 q, 2 H (N—CH_2); 5·12 s, 1 H (C(4)-H); 7·1–8·2 m, 7 H (carbazole protons); 8·9 sb, 1 H (NH-DHP)
VI	CD_3SOCD_3: 2·32 s, 6 H (2 Me); 3·62 s, 6 H (2 OMe); 5·3 s, 1 H (C(4)-H); 7·4–8·5 m, 5 H (quinoline protons); 9·1 sb, 1 H (NH-DHP)
VII	CD_3SOCD_3: 2·31 s, 6 H (2 Me); 3·41 s, 6 H (2 OMe); 5·39 s, 1 H (C(4)-H); 7·1–8·4 m, 5 H (quinoline protons); 9·06 sb, 1 H (NH-DHP); 11·6 sb, 1 H (OH quinoline)
VIII	$CDCl_3$: 2·35 s, 6 H (2 Me); 2·75 s, 3 H (Me quinoline); 3·41 s, 6 H (2 OMe); 5·7 s, 1 H (C(4)-H); 6·2 sb, 1 H (NH-DHP); 7·35 d, 1 H (C(3′)-H, J = 8·8); 7·5–7·9 m, 3 H (quinoline protons); 8·85 d, 1 H (C(4′)-H, J = 8·8)
IX	$CDCl_3$: 1·15 t, 6 H (2 OEt, J = 7); 1·35 q, 3 H (N-Et, J = 7); 2·28 s, 6 H (2 Me); 2·58 s, 3 H (C(5′)-Me); 3·9–4·3 m, 6 H (2 OEt, N-Et); 5·9 s, 1 H (C(4)-H); 6·54 sb, 1 H (NH-DHP)
X	$CDCl_3$: 1·25 t, 6 H (2 OEt, J = 7); 1·45 t, 3 H (N-Et, J = 7); 2·28 s, 6 H (2 Me); 2·5 s, 3 H (C(3′)-Me); 4·02 q, 4 H (2 OEt, J = 7); 4·15 q, 2 H (N-Et, J = 7); 6·1 s, 1 H (C(4)-H); 6·2 sb, 1 H (NH-DHP)
XI	CD_3SOCD_3: 1·1 t, 6 H (2 OEt, J = 7); 2·38 s, 6 H (2 Me); 2·53 s, 3 H (C(5′)-H); 3·71 s, 3 H (N-Me); 4·0 q, 4 H (2 OEt); 5·7 s, 1 H (C(4)-H); 8·5 sb, 1 H (NH-DHP)
XII	$CDCl_3$: 1·18 t, 6 H (2 OEt); 2·3 s, 6 H (2 Me); 2·48 s, 3 H (C(3)-H); 4·0 s, 3 H (N-Me); 3·9–4·1 q, 4 H (2 OEt); 5·6 s, 1 H (C(4)-H); 6·2 sb, 1 H (NH-DHP)
XIII	$CDCl_3$: 1·5 q, 3 H (N-Et, J = 7); 2·27 s, 6 H (2 Me); 2·5 s, 3 H (C(3′)-Me); 3·58 s, 6 H (2 OMe); 4·22 q, 2 H (N-Et, J = 7); 5·82 s, 1 H (C(4)-H); 6·2 s, 1 H (NH-DHP)
XIV	$CDCl_3$: 1·35 q, 3 H (N-Et, J = 7); 2·28 s, 6 H (2 Me); 2·55 s, 3 H (C(5′)-Me); 3·58 s, 6 H (2 OMe); 4·03 q, 2 H (N-Et, J = 7); 5·8 s, 1 H (C(4)-H); 6·4 sb, 1 H (NH-DHP)
XV	CD_3SOCD_3: 2·35 s, 6 H (2 Me); 3·48 s, 6 H (2 OMe); 5·71 s, 1 H (C(4)-H); 7·6 d, 1 H (C(3′)-H, J = 4·8); 7·81 t, 1 H (C(6′)-H); 8·22 d 3 H (C(5′)-H, J = 7·2); 8·79 d, 1 H (C(7′)-H); 8·92 d, 1 H (C(2′)-H, J = 4·8); 9·15 sb, 1 H (NH-DHP)
XVI	$CDCl_3$: 2·28 s, 6 H (2 Me); 3·4 s, 6 H (2 OMe); 6·16 s, 1 H (C(4)-H); 7·7–7·9 m, 3 H (quinoxaline protons); 8·63 sb, 1 H (NH-DHP); 8·8 d (C(3′)-H, J = 1·6); 8·92 d, 1 H (C(2′)-H)

TABLE III

Pharmacological activity of compounds *II*—*XVI*

Compound	Negative inotropic activity[a]	Negative chronotropic activity[b]	Calcium antagonist activity[c]	ED50 inotropic negative potency		ED30 chronotropic negative potency		IC50 calcium antagonist potency	
				ED50[d] μM/l	95% conf. lim. (. 10^{-6})	ED30[d] μM/l	95% conf. lim. (. 10^{-6})	IC50[d] μM/l	95% conf. lim. (. 10^{-6})
II	39 ± 2·7	28 ± 3·6	39 ± 2·9						
III	49 ± 3·4	76 ± 2·4[2]	78 ± 2·7			1·1	0·7—1·9	4·1	3—5·6
IV	23 ± 2·9[1]	14 ± 2·8	9 ± 0·5						
V	3·7 ± 1·8	18 ± 3·3	1·4 ± 0·4						
VI	16 ± 3·5	13 ± 2·4	7·5 ± 1·8						
VII	2·3 ± 1·2	42 ± 3·4	8·6 ± 1·7						
VIII	60 ± 4·2	95 ± 2·7[2]	89 ± 2·6	17	7·6—29	0·6	0·2—1·5	2·3	1·7—3·1
IX	30 ± 1	95 ± 3[3]	56 ± 2·6			0·6	0·4—0·7		
X	75 ± 2·9	90 ± 4·6[3]	53 ± 1·4	15	7·6—20	0·63	0·2—1·6		
XI	27 ± 2·8	6 ± 1·3	32 ± 2·3						
XII	85 ± 3·4	92 ± 4·2[4]	54 ± 2·9	4·9	3·5—7	0·05	0·04—0·06		
XIII	67 ± 2·7	95 ± 3·2	96 ± 3[5]	7·2	3·1—17	0·75	0·44—1·20	2·8	2·1—3·7
XIV	35 ± 3·4	45 ± 2·8	81 ± 2·3					23	12—35
XV	8·5 ± 1·5	80 ± 3·5	85 ± 3·1			2·4	1·4—4	6·8	3·6—13
XVI	86 ± 1·9	100[2]	100[6]	2·6	1·3—5·3	1·66	0·95—2·9	5·8	4·2—8·1
Nifedipine	97 ± 2[7]	85 ± 4·2[8]	82 ± 1·3[9]	0·27	0·19—0·36	0·02	0·01—0·03	0·009	0·003—0·02

[a] On isolated guinea-pig left atrium. The decrease in atrial rate at 5 . 10^{-5} mol/l is expressed as % changes from control ± S.E.M. ($n = 5—6$). The left atria were driven at 1 Hz and the 5 . 10^{-5} mol/l conc. gives the maximum effect for most compounds. [b] On isolated guinea-pig spontaneously beating right atrium. The decrease in atrial rate at 5 . 10^{-5} mol/l is expressed as % changes from control ± S.E.M.($n = 5—6$). The right atria were spontaneously beating and the 5 . 10^{-5} conc. gives the maximum effect for most compounds. Pretreatment ranged from 165 to 185 beat/min. [c] % Inhibition of calcium contraction (80 mM-KCl) at 10^{-4} mol/l conc. which gives the maximum effect for most compounds. Values are means ± S.E.M. ($n = 6—7$). [d] Calculated from log concentration–response curves. (Probit analysis by Litchfield and Wilcoxon with $n = 6—8$)

[1] Positive inotropic activity. [2] At the 10^{-5} mol/l conc. (complete standstill at the 5 . 10^{-5} mol/l conc. 2 out of 6 experiments). [3] At the 5 . 10^{-6} mol/l conc. (complete standstill at the 10^{-5} mol/l conc. 2 out of 6 experiments). [4] At the 5 . 10^{-7} mol/l conc. (complete standstill at 10^{-6} mol/l 4 out of 6 experiments). [5] At the 5 . 10^{-5} mol/l conc. [6] At the 5 . 10^{-4} mol/l conc. [7] At the 10^{-5} mol/l conc. [8] At the 10^{-7} mol/l conc. nifedipine produced a complete standstill 4 out of 6 experiments. [9] At the 10^{-6} mol/l conc.

compounds *VIII–X*, *XII*, *XIII* are weak calcium antagonists and stronger negative inotropic agents. Moreover the doses effective in antagonizing calcium in vascular smooth muscle are some hundred times greater than those giving negative chronotropic acitivity (Table III).

Although this may due to tissue selectivity, the results taken as a whole seem to indicate that the potent bradycardic effects may also due to other mechanism beside calcium antagonism.

In conclusion, the more active compounds (*VIII–X*, *XII*, *XIII*) show a significant negative inotropic activity and a rather specific bradycardic action localized in the heart.

EXPERIMENTAL

Melting points were determined with a Büchi capillary apparatus and are uncorrected. Nuclear magnetic resonance spectra were determined for solution in $CDCl_3$ or CD_3SOCD_3 with a Brucker AC 200 spectrometer (200 MHz). Chemical shifts are given in ppm (δ-scale), coupling constants (J) in Hz. In IR spectra wavenumbers are given in cm^{-1}. All the compounds described gave rise to a single spot on TLC with three different solvents systems of low, medium and high polarity.

The known carboxaldehydes were prepared according to literature methods; 1*H*-indole-2-carboxaldehyde[11], 1-benzyl-5-nitro-1*H*-benzimidazole-2-carboxaldehyde[12], 9-ethyl-9*H*-carbazole-3-carboxaldehyde[13], 8-nitroquinoline-2-carboxaldehyde[14], 1,3-dimethyl-4-nitro-pyrazole-5--carboxaldehyde[8], 1,5-dimethyl-4-nitro-pyrazole-3-carboxaldehyde[8], 8-nitroquinoline-4-carboxaldehyde[15].

Ethyl 2-Methylquinoline-5-carboxylate

A mixture of 2-methylquinoline-5-carboxylic acid[16] (1 g, 5·3 mmol) in anhydrous ethanol (100 ml), containing a few drops of concentrated sulfuric acid, was refluxed for 6 h. After cooling and addition of water (20 ml), the solution was alkalinized with 2M-NaOH. The resulting white precipitate was collected by filtration and crystallized from methanol to give 0·9 g (87% yield) melting at 50–51°C. IR (Nujol) : 1 715 (CO). For $C_{13}H_{13}NO_2$ (215·25) calculated: 72·54% C, 6·09% H, 6·51% N; found: 72·34% C, 5·99% H, 6·41% N.

2-Methylquinoline-5-methanol

A solution of ethyl 2-methylquinoline-5-carboxylate (1 g, 4·64 mmol) in 5 ml dry THF was added dropwise to an ice-cooled and stirred suspension of $LiAlH_4$ (0·176 g, 4·64 mmol) in THF (12 ml). After standing 1 h at room temperature the reaction mixture was quenched carefully by water (10 ml). The mixture was extracted with ethyl ether (3 × 20 ml) and the combined organic layers were washed with brine, dried on anhydrous sodium sulfate and evaporated in vacuo. The crude product obtained was crystallized from ethyl acetate–petroleum ether 1 : 1 to give 0·6 g of the corresponding alcohol melting at 120–122°C. ^1H NMR ($CDCl_3$): 2·72 s, 3 H (C(2)-Me); 5·02 m, 2 H (CH_2OH); 5·2 mb, 1 H (OH); 7·3–8·4 m, 5 H (quinoline protons). For $C_{11}H_{11}NO$ (173·22) calculated: 76·28% C, 6·40% H, 8·09% N; found: 76·23% C, 6·34% H, 7·95% N.

2-Methylquinoline-5-carboxaldehyde

Manganese dioxide (2 g, 23 mmol) was added portionwise to a solution of 2-methylquinoline-5--methanol (1 g, 5·77 mmol) in chloroform (20 ml). The reaction mixture was refluxed for 12 h, filtered and the filtrate was evaporated under reduced pressure. The crude product obtained was purified by column chromatography on silica gel eluting with ethyl acetate–petroleum ether solutions (6 : 4) to give the solid aldehyde in turn crystallized from ethyl acetate to give 0·53 g (54 %) melting at 60—62°C. IR (Nujol): 1 675 (CO). ^{1}H NMR ($CDCl_3$): 2·78 s, 3 H (C(2)-Me); 7·47 d, 1 H (C(3)-H, J = 8·8); 7·84 m, 1 H (C(7)-H); 7·99 m, 1 H (C(6)-H); 8·27 m, 1 H (C(8)-H); 9·47 d, 1 H (C(4)-H, J = 8·8); 10·33 s, 1 H (CHO). For $C_{11}H_9NO$ (171·2) calculated: 77·17% C, 5·30% H, 8·18% N; found: 77·01% C, 5·21% H, 8·12% N.

2-Hydroxyquinoline-4-carboxaldehyde

The compound was prepared by selenium dioxide oxidation of commercially available 4-methyl-2--quinoline. The product was purified by column chromatography on silica gel eluting with chloroform–methanol (5 : 1) and crystallized from methanol to give 1·5 g (69%) melting at 280—281°C. IR (Nujol): 1 707 (CO). ^{1}H NMR ($CDCl_3$): 7·2—8·4 m, 6 H (quinoline protons and OH); 11·20 s, 1 H (CHO). For $C_{10}H_7NO_2$ (173·2) calculated: 69·36% C, 4·07% H, 8·09% N; found: 68·72% C, 3·89% H, 7·92% N.

Quinoxaline-5-carboxaldehyde

A solution of N-bromosuccinimide (3·68 g, 20 mmol), 5-methylquinoxaline (1 g, 6·9 mmol) and a little amount of benzoyl peroxide in carbon tetrachloride (35 ml) was refluxed for 2 h while irradiated with 159-W tungsten-filament lamp in an aluminium reflector. After cooling and filtration, the solution was evaporated under reduced pressure giving a solid residue which, after crystallization from ethanol (1·25 g; 81%), was hydrolyzed directly to carboxaldehyde by refluxing an aqueous alcoholic solution for 3 h in the presence of freshly precipitated calcium carbonate. The mixture was filtered and evaporated in vacuo and the crude product was purified by crystallization from ethanol to give 0·5 g (71·4%) of a white solid melting at 125—126°C. IR (Nujol): 1 673 (CO). ^{1}H NMR ($CDCl_3$): 7·7—8·0 m, 3 H (quinoxaline protons); 8·8 d, 1 H (C(3)-H; 8·92 d, 1 H (C(2)-H); 11·24 s, 1 H (CHO). For $C_9H_6N_2O$ (158·16) calculated: 68·35% C, 3·82% H, 17·71% N; found: 68·12% C, 3·75% H, 17·56% N.

1-Ethyl-3-methyl-4-nitropyrazole-5-carboxaldehyde

This compound was prepared according to the methodology depicted in Scheme 2 and reported in our previous paper[8]. Oil; 65% yield. ^{1}H NMR ($CDCl_3$): 1·45 t, 3 H (N-Et, J = 7); 2·59 s, 3 H (C 3-Me); 4·52 q, 2 H (N-Et, J = 7); 10·45 s, 1 H (CHO).

1-Ethyl-5-methyl-4-nitropyrazole-3-carboxaldehyde

This compound was prepared according to the methodology depicted in Scheme 2 and reported in our previous paper[8]. Oil; 53% yield. ^{1}H NMR ($CDCl_3$): 1·51 t, 3 H (N-Et, J = 7); 2·71 s, 3 H (C 3-Me); 4·27 s, 2 H (N-Et, J = 7); 10·43 s, 1 H (CHO).

General Procedure for the Preparation of Dialkyl
1,4-Dihydro-2,6-dimethyl-4-(heteroaryl)-3,5-pyridinedicarboxylates (*II*—*XVI*)

The appropriate alkyl acetoacetate (0·02 mol) was added to a solution of the corresponding

heterocyclic carboxaldehyde (0·01 mol) in ethanol of isopropanol (entries *IX*—*XIV*) and then ammonium hydroxide (1·4 ml, 0·04 mol, 30% w/v) was added with stirring. The yellow mixture was heated under reflux for 10 h, cooled at room temperature and evaporated to dryness in vacuo. The crude product was chromatographed on a silica gel column eluting with ethyl acetate–hexane and/or crystallized from a suitable solvent (Table I).

REFERENCES

1. Vanhoutte P. M., Paoletti R.: T.I.P.S. *8*, 4 (1987).
2. Kendall H., Luscombe D. K.: Prog. Med. Chem. *24*, 249 (1987).
3. Janis R. A., Scher P. J., Triggle D. J.: Adv. Drug Res. *16*, 309 (1987).
4. Sausins A., Duburs G.: Heterocycles *27*, 269 (1988).
5. Verde M. J., Del Sol G., Fernandez G., Sabano A.: *Acta del Primer Congreso conjunto Hispano-Italiano de Quimica Terapeutica, 19—22 September, Granada 1989;* p. 93.
6. Prous J., Blancofort P., Castaner J., Serradell M. N., Mealy N.: Drugs Fut. *5*, 427 (1981).
7. Hof R. P., Salzman R., Sreyl H.: Am. J. Cardiol. *59*, 308 (1987).
8. Baraldi P. G., Chiarini A., Budriesi R., Dasolari A., Manfredini S., Simoni D., Zanitaro V., Varani K., Borea P. A.: Drug Design. Delivery *5*, 13 (1989).
9. Garuti L., Ferranti A., Burnelli S., Varoli L., Giovanninetti G., Brigidi P., Casolari A.: Bull. Chim. Farm. *128*, 136 (1989).
10. Tallarida J., Murray R. B.: *Manual of Pharmacologic Calculations with Computer Programs*, 2nd ed. Springer, New York 1987.
11. Doyle F. P., Ferrier W., Holland D. O., Mehta M. D., Nayler J. H. C.: J. Chem. Soc. *1956*, 2853.
12. Garuti L., Giovanninetti G., Ferranti A., Chiarini A., Bertocchi G., Sabatino P., Brigidi P.: Pharmazie *42*, 378 (1987).
13. Buu-Hoi Ng. Ph., Hoan Ng.: J. Org. Chem. *16*, 1327 (1951).
14. Shoeb H. A., Korkor M. I., Tammam G. H.: Pharmazie *33*, 581 (1978).
15. Johnson O. H., Hamilton C. S.: J. Am. Chem. Soc. *63*, 2864 (1941).
16. Leir C. M. (Riker Laboratories, Inc.): U.S. 4.565.872 (1986); Chem. Abstr. *105*, 42671 (1986).