Cardiotonic Agents. 2. Synthesis and Structure–Activity Relationships in a New Class of 6-, 7-, and 8-Pyridyl-2(1*H*)-quinolone Derivatives

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A series of 6-, 7-, and 8-pyridyl-2(1*H*)-quinolone derivatives with various quinolone substitutents (CH_3, Cl, OH, OCH_3) was prepared by arylation of pyridine with quinolone via a diazotized aminoquinolone for positive inotropic activity. Several derivatives, especially those with a pyridyl ring in the 6-position, were from 28 to 50 times more potent on left guinea pig atria than ARL-115 and milrinone used as references. Intrinsic activities of the derivatives were almost equivalent to that of ARL-115. These results indicate that pyridyl-2(1*H*)-quinolone derivatives are a potent new class of positive inotropic agents.

In a previous paper,[1] we reported the synthesis and the cardiotonic activities of a new series of 3-, 4-, and 5-pyridyl-2(1*H*)-quinolone derivatives. In those compounds we combined the important structural features of the quinolone nucleus with the pyridyl ring encountered in a variety of cardiotonic agents such as amrinone,[2] milrinone,[3] and piroximone.[4]

We have now extended our work to the synthesis of quinolone derivatives of general structure **A** (Chart I) substituted with a pyridyl ring in the 6-, 7-, and 8-positions, and we discuss some structure–activity relationships.

Chemistry

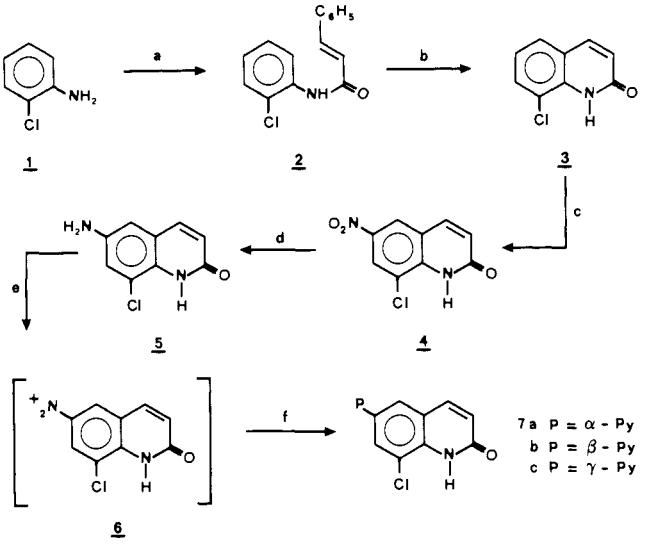
Our approach toward the preparation of compound **A** (R = Cl) involved, as a key step, the arylation of pyridine with quinolone via a diazotized aminoquinolone as shown in Scheme I.

8-Chloro-2-quinolone (**3**) was prepared from cinnamanilide (**2**) by a known method.[5] Nitration of **3** in AcOH gave only the 6-nitro isomer **4** as could be expected from the para-orienting effect of the quinolone lactam group. The nitro group of **4** was then reduced with $SnCl_2$ to give **5**, which was finally diazotized and added to pyridine[1,6] to give a mixture of α, β, and γ isomers **7a–c** respectively, purified by column chromatography.

The structure of each position isomer was identified unambiguously from the H_α pyridyl signals in the NMR of **7a** (δ 8.8 (m, 1 H)) and **7b** (δ 8.5 (m, 2 H)) whereas, in **7c**, pyridyl hydrogens appear as two doublets (δ 7.3 (d, 2 H, J = 6 Hz), 8.7 (d, 2 H, J = 6 Hz)).

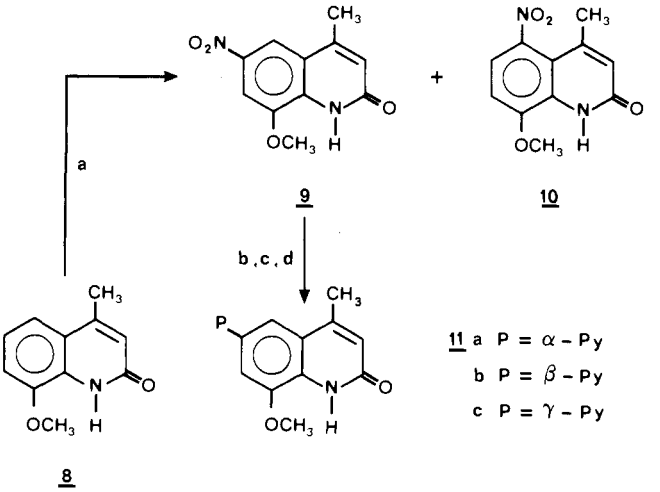
Compounds **11a–c** with a 4-methyl and an OCH_3 group in the 8-position of the 2-quinolone nucleus were prepared following Scheme II. Nitration of 4-methyl-8-methoxy-2-quinolone (**8**) gave a mixture of nitro isomers[1] **9** and **10** (ca. 80%) in which the 6-nitro isomer predominated (ca. 60%). Reduction of **9** with $SnCl_2$ gave the 6-amino derivative, which was subjected to diazotization, and the diazonium intermediate was added to pyridine to give **11a–c**. We have already noted[1] that 3,4-dihydropyridylquinolones could not be obtained from the corresponding aromatic analogue because the pyridyl ring suffered hydrogenation before the 3,4 double bond of the quinolone nucleus. The desired 3,4-dihydroquinolones **16a–c** and **17a–c** (Scheme III) were therefore obtained from the 6-nitro precursor **14**, the only isomer formed in the nitration of **13** providing evidence for the strong para-orienting effect of the lactam group and the poor directing effect of the 8-OCH_3 group. A mixture of isomers **16a–c** was obtained in the last step. The Clauss and Jensen method,[7] involving demethylation with 48% HBr, mesylation, and catalytic hydrogenation, was used to prepare 8-unsubstituted compounds **17a–c**.

Scheme I[a]



[a] Key: py = pyridine; a = $C_6H_5CH{=}CHCOCl$; b = $AlCl_3/C_6H_5Cl$; c = $HNO_3/AcOH$; d = $SnCl_2/HCl$; e = $NaNO_2/HCl$; f = pyridine.

Scheme II[a]



[a] Key: py = pyridine; a = $HNO_3/Ac_2O/AcOH$; b = $SnCl_2/HCl$; c = $NaNO_2/HCl$; d = pyridine.

The strategy adopted for the preparation of unsubstituted 6-, 7-, and 8-pyridylquinolones **22a–c**, **23a,b**, and **24b**

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(1) Leclerc, G.; Marciniak, G.; Decker, N.; Schwartz, J., preceding paper in this issue.
(2) Alousi, A. A.; Farah, A. E.; Lesher, G. Y.; Opalka, C. J. *Circ. Res.* **1972**, *45*, 666.
(3) Alousi, A. A.; Staukus, G. P.; Stuart, J. C.; Walton, L. H. *J. Cardiovasc. Pharmacol.* **1983**, *5*, 804.

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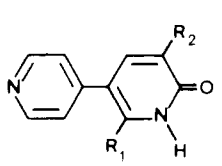
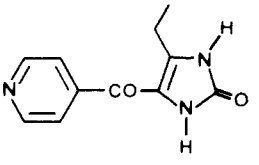
Chart I

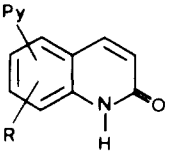


amrinone $R_1 = H$, $R_2 = NH_2$

milrinone $R_1 = CH_3$, $R_2 = CN$

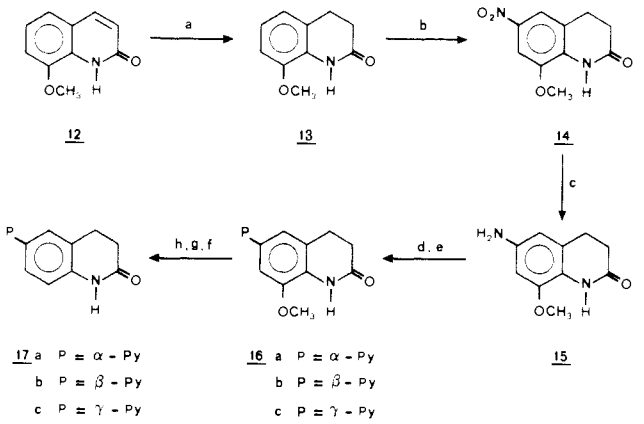


piroximone



A

Scheme III[a]



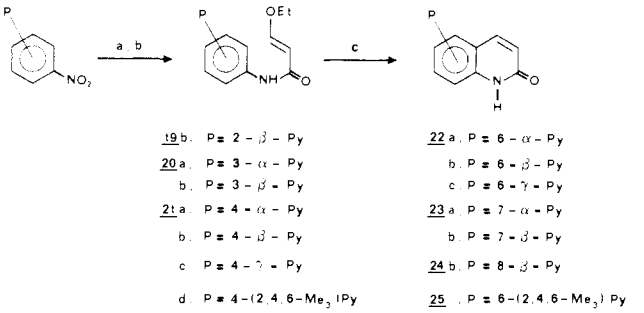
12 13 14 15

17 a P = α-Py; b P = β-Py; c P = γ-Py

16 a P = α-Py; b P = β-Py; c P = γ-Py

[a] Key: py = pyridine; a = $H_2/Rh/Al_2O_3$; b = $HNO_3/Ac_2O/AcOH$; c = H_2/PtO_2; d = $NaNO_2/HCl$; e = pyridine; f = HBr, Δ; g = MesCl; h = $H_2/Pd/C$.

Scheme IV[a]



19 b. P = 2-β-Py

20 a. P = 3-α-Py; b. P = 3-β-Py

21 a. P = 4-α-Py; b. P = 4-β-Py; c. P = 4-γ-Py; d. P = 4-(2,4,6-Me_3)Py

22 a. P = 6-α-Py; b. P = 6-β-Py; c. P = 6-γ-Py

23 a. P = 7-α-Py; b. P = 7-β-Py

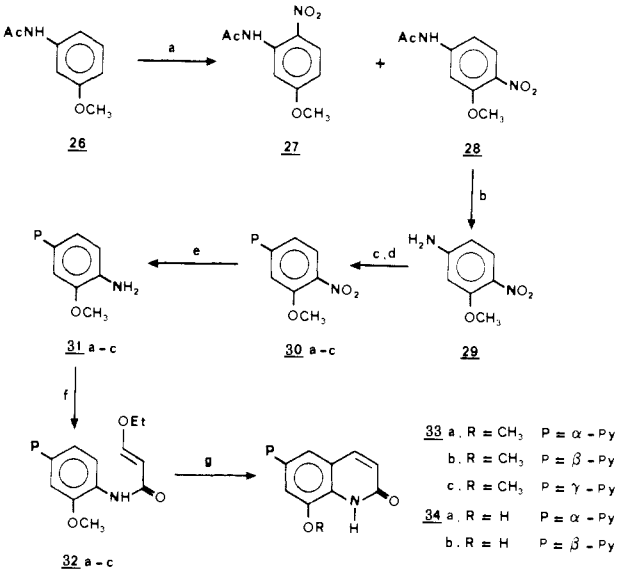
24 b. P = 8-β-Py

25 . P = 6-(2,4,6-Me_3) Py

[a] Key: py = pyridine or 2,4,6-trimethylpyridine; a = $SnCl_2$, HCl; b = EtOCH = CHCOCl; c = H_2SO_4.

is depicted in Scheme IV. The pyridyl moiety was introduced at an early stage. (Nitrophenyl) pyridyl isomers[6] were purified and used as building blocks for the elaboration of the quinolone nucleus following the sequence $SnCl_2$ reduction, anilide formation, and H_2SO_4 cyclization. As expected, *m*-nitroaniline gave rise to a mixture of 5-pyridyl-2-quinolone (12%) and 7-pyridyl-2-quinolone (64%) as evidenced by the NMR of the latter that showed a deshielded signal (1 H) at δ 8.6 (J = 2 Hz) for the 8-H. This assignment was confirmed by the fact that the 5-pyridyl analogue had previously been prepared[1] from 5-pyridyl-8-methoxy-2-quinolone. The (2,4,6-trimethylpyridyl)quinolone (**25**) was prepared in the same manner as described in Scheme IV.

Scheme V[a]



26 27 28 29

31 a-c 30 a-c

32 a-c

33 a. R = CH_3 P = α-Py; b. R = CH_3 P = β-Py; c. R = CH_3 P = γ-Py

34 a. R = H P = α-Py; b. R = H P = β-Py

[a] Key: py = pyridine; a = $HNO_3/Ac_2O/AcOH$; b = HCl; c = $NaNO_2/HCl$; d = pyridine; e = $SnCl_2/HCl$; f = EtOCH=CHCOCl; g = H_2SO_4.

Finally, compounds **33a–c** and **34a,b** were prepared as depicted in Scheme V. Nitration of acetyl-*m*-anisidine in AcOH has been reported[8] to give a mixture of isomers from which **29** was isolated in 12% yield. In our hands, this reaction failed to give the desired product.[9] However, compound **29** was obtained by nitration of **26** in excess $Ac_2O/AcOH$ with 1 equiv of nitric acid. By the same sequence as in Scheme I, pyridyl quinolones **33a–c** were obtained.

The 8-methoxy group was removed from **33a,b** as before to give **34a,b**. Alkylation of **22b** (NaH, DMF, 2-morpholinoethyl chloride) led to an ~3:1 mixture of N- and O-alkylated products **35** and **36** identified by NMR and IR. Similarly, the *N*-methyl analogue **37** was prepared.

Biological Results and Discussion

Compounds of type **A** were evaluated on isolated left quinea pig atria for positive inotropic activity, as described in the Experimental Section. The dose of each compound

(4) Schnettler, R. A.; Dage, R. C.; Grisar, J. M. *J. Med. Chem.* **1982**, *25*, 1477.
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(7) Clauss, K.; Jensen, H. *Angew. Chem.* **1973**, *85*, 981.
(8) Reverdin, F.; Widmer, K. *Ber.* **1913**, 4066.
(9) More drastic conditions (>65 °C) led to 2,4-dinitro-5-methoxyphenol (ca. 20%). The structure was elucidated from the NMR that revealed two aromatic signals (1 H) at δ 6.68 and 8.82 in addition to a methoxy group at δ 4.02 and a deshielded and exchangeable signal at δ 11.1 for the OH group. Mass spectra confirmed the structure (m/e 214) as did microanalysis. The mechanism for the formation of this phenol might involve "nitrosation" of the anilide **26** or of a nitro analogue (via the decomposition of nitric acid into N_2O_4, with the subsequent formation of HNO_2 with H_2O) followed by rearrangement into a phenolacetate and hydrolysis. The different course followed by the reaction in the presence of Ac_2O might thus be explained by the trapping of water required for the dismutation of N_2O_4 into HNO_3 and HNO_2.

required to produce 50% of the maximum effect is shown in Table I.

Among the compounds in Table I, 6-pyridylquinolone derivatives were consistently more potent inotropic agents than the 7- and 8-pyridyl analogues **23b** and **24b**. The ED_{50} for 6-pyridylquinolone derivatives varied from 2.8×10^{-7} to 1.9×10^{-5} M, with intrinsic activities between 0.45 and 0.88.

We then explored the effects of substituents on the aromatic ring of **22a–c** in an attempt to optimize inotropic activity. 8-Chloro compounds **7a**, **7b**, and **7c** were more potent positive inotropic agents than their unsubstituted analogues **22a**, **22b**, and **22c**. 8-OH-substituted quinolones **34a** and **34b** were nearly equipotent to the parent analogues **22a** and **22b**. In contrast, introducing a 8-OCH_3 substituent (**33b**, **33c**) led to a reduction in potency. We also noted the highly detrimental influence of the 4-Me substituent in the β-pyridyl series. The ED_{50} of **11b** was 32 times lower than that of the unsubstituted compound **22b** and 2.5 times lower than that of the 8-OCH_3 analogue **33b**. The noteworthy potency and intrinsic activities of the 2,4,6-trimethyl analogue **25** were half those of **22b**. We also studied the influence of hydrogenation of the 3,4 double bond upon the inotropic activity. In the unsubstituted series, this effect was weak, and the activities of **17b** and **17c** were comparable with those of **22b** and **22c**. However, in the 8-OCH_3 series, this hydrogenation drastically decreased the affinity of the β-pyridyl compound **16b**, respectively, by 68 and 5 times compared with **22b** and **33b**.

To examine whether the presence of a secondary lactam[10] was a major factor in determining inotropic potency, we prepared N- and O-substituted analogues. The *N*-methyl compound **37** had weak inotropic activity; indeed, its affinity and intrinsic activity were 220 and 2 times less than those of **22b**. Similarly, the affinity of the *N*-morpholinoethyl analogue **35** was reduced by a factor of 44, although its intrinsic activity was almost equal to that of **22b**. The *O*-morpholinoethyl analogue **36** was even less active. Finally, the 6-amino derivative **5** was barely active.

Table I also shows, for the sake of comparison, the inotropic responses of ARL-115[11] and of milrinone.[3] Derivatives **7a**, **7b**, **22b**, and **34b** were from 28 to 50 times more potent than ARL-115 and milrinone. The affinities of most other molecules were still higher or at least equal to those of the references. More often, the intrinsic activities of the quinolone derivatives were almost equivalent to that of ARL-115.

In summary, these results, and those presented in the preceding paper,[1] confirm that the pyridyl nucleus in compounds **A** is required for positive inotropic activity. In all series, the β-nitrogen position appears to give the best potency (**7b**, **22b**, **34b**) as Robertson et al.[12] noted for arylimidazopyridine cardiotonics. Furthermore, the position of the pyridyl nucleus on the quinolone affects the potency in the following order **6** ≥ **5** = **7** > **4** > **8** > **3**. Otherwise, the secondary lactam function was vital for a significant cardiotonic activity.[10] Finally, substituents at the 8- and (or) at the 4-position on the quinolone nucleus were not requisite, and the 6-pyridylquinolone series was the most suitable for the nature of the substituents as well as for the hydrogenation of the 3,4 double bond.

In conclusion, 5- and 6-pyridyl-2(1*H*)-quinolone derivatives are a potent new class of positive inotropic agents. Further detailed pharmacological studies of these series are in progress and will be reported subsequently.

Experimental Section

Chemistry. Melting points (mp ±1 °C) were obtained on a calibrated Kofler hot-stage apparatus and are uncorrected. Infrared spectra were measured in $CHCl_3$ solution with a Beckman IR 33 spectrophotometer. NMR (60-MHz) spectra were recorded on a Perkin-Elmer spectrometer using Me_4Si in a capillary as an external reference.

8-Chloro-2-quinolone (3). To an ice-cooled solution of 2-chloroaniline (**1**; 8.1 g, 635 mmol) in benzene (60 mL) containing pyridine (5 mL) was added cinnamoyl chloride (10 g, 60 mmol) in benzene (60 mL) dropwise with stirring. After 12 h, EtOAc was added until dissolution occurred, and the mixture was washed with water, dilute hydrochloric acid (2 × 75 mL), and aqueous $NaHCO_3$. The dried organic layer on concentration gave the amide **2**, which was used as such in the next step.

To a solution of **2** (8.26 g, 32 mmol) in chlorobenzene (50 mL) was added portionwise under stirring $AlCl_3$ (21.4 g, 160 mmol). The mixture was heated to 125 °C and maintained at this temperature for 3 h. Then, the solution was carefully poured onto ice; the precipitate formed was triturated with hexane and filtered to give practically pure **3**: yield 5.6 g (97%); mp 208 °C. Anal. (C_9H_6ClNO) C, H, N.

8-Chloro-6-nitro-2-quinolone (4). The above quinolone **3** (28 g, 156 mmol) was dissolved in AcOH (150 mL). Fuming HNO_3 (56.6 mL) was added, and the mixture was heated under reflux for 1.5 h. After cooling, the solution was poured onto ice–water (ca. 800 mL). The solid was collected and washed successively with water (2 × 150 mL), 5% $KHCO_3$ (2 × 150 mL), and water (2 × 100 mL): yield 29 g of **4** (83%); mp >260 °C; NMR (Me_2SO-d_6) δ 5.92 (1 H, d, vinyl H, $J \cong 10$ Hz), 7.34 (1 H, d, vinyl H, J = 10 Hz), 7.59 (1 H, d, Ar H, J = 2 Hz), 7.85 (1 H, d, Ar H, J = 2 Hz). Anal. ($C_9H_5ClN_2O_3$) C, H, N.

6-Amino-8-chloro-2-quinolone (5). To a solution of **4** (26.96 g, 120 mmol) in MeOH (168 mL) was added carefully a solution of $SnCl_2$ (83.9 g of $SnCl_2 \cdot 2H_2O$) in concentrated HCl (67.7 mL). After the mixture was heated at 60 °C for 2.5 h and then at 90 °C for 2.5 h, a solution of 20% $KHCO_3$ (1.2 L) was added. The yellow suspension was stirred with EtOAc (400 mL); the aqueous phase was filtered on Celite and extracted four times with EtOAc. The green Celite cake was thoroughly extracted with $CHCl_3$ in a Soxhlet apparatus. The combined organic extracts were dried, filtered, and evaporated to give crude **5** (24 g), which was purified by dissolving in 1 N HCl (140 mL) and extracting with $CHCl_3$ (4 × 100 mL). The aqueous solution was alkalinized with $KHCO_3$, and the yellow precipitate was filtered to give 21 g (90%) of purified **5**: mp 193 °C; NMR (Me_2SO-d_6) δ 5.2 (2 H, m, NH_2, exchangeable D_2O), 6.48 (1 H, d, vinyl H, J = 9 Hz), 6.72 (1 H, d, Ar H, J = 2 Hz), 7.00 (1 H, d, ArH, J = 2 Hz), 7.72 (1 H, d, vinyl H, J = 9 Hz), 10.55 (1 H, m, CONH, exchangeable D_2O). Anal. ($C_9H_7ClN_2O$) C, H, N.

8-Chloro-6-pyridyl-2-quinolones 7a–c. A solution of **5** (7.8 g) in a mixture of 11 N HCl (14.3 mL) and water (10.0 mL) was diazotized at below 0 °C with a solution of $NaNO_2$ (2.8 g) in water (7 mL). The resulting cold diazonium suspension was then dropped into pyridine (40 mL) and stirred at 80 °C. After 1 h, the mixture was cooled, 33% NH_4OH (10.4 mL) was added, and the solvents were evaporated under reduced pressure. The residue was suspended in 10% $KHCO_3$ (100 mL) and extracted with $CHCl_3$. The organic phase was filtered on Celite, dried, and evaporated to give a mixture of **7a–c** as a brown powder. Column chromatography on silica gel (300 g) eluting with $CHCl_3$/EtOAc/MeOH (46:50:4) gave 1.7 g (16.5%) of 8-chloro-6-α-pyridyl-2-quinolone (**7a**), 0.6 g (5.8%) of 8-chloro-6-β-pyridyl-2-quinolone (**7b**), and 0.6 g (5.8%) of 8-chloro-6-γ-pyridyl-2-quinolone (**7c**).

8-Methoxy-4-methyl-6-pyridyl-2-quinolones 11a–c. Nitration of **8** in HNO_3/Ac_2O/AcOH as previously described[1] gave **9** (ca. 40%), which was reduced with $SnCl_2$, diazotized, and added to pyridine, as described above, to give a mixture of **11a–c**. It was purified by column chromatography eluting with EtOAc/MeOH (90:10) to give **11a** (12%) and a mixture of **11b** and **11c**,

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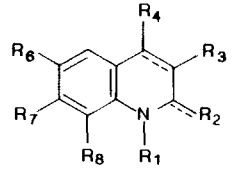
(11) Dahmen, M.; Greeff, K. *Arzneim.-Forsch.* **1981**, *31*, 161.
(12) Robertson, D. W.; Beedle, E. E.; Knishinski, J. H.; Pollock, G. D.; Wilson, H.; Wyss, V. L.; Hayes, J. H. *J. Med. Chem.* **1985**, *28*, 717.

Table I. Physicochemical Data and Positive Inotropic Effects in Isolated Left Guinea Pig Atria of Quinolone



A

compd	R_1	R_2	R_3	R_4	R_6	R_7	R_8	mp,[a] °C	cryst solvent	yield,[b] %	empirical formula[c]	inotropic activity: ED_{50} ± SEM, M	inotropic activity: int act.[d] ± SEM (*n*)
5	H	CO	H	H	NH_2	H	Cl	193	EtOH/H_2O	33.0	$C_9H_7ClN_2O$·HCl	(1.0 ± 0.5) × 10^{-4}	0.54 ± 0.12 (4)
7a	H	CO	H	H	α-py	H	Cl	206	2-PrOH/MeOH	5.5	$C_{14}H_9ClN_2O$·$C_2H_2O_4$	(2.05 ± 1.0) × 10^{-6}	0.75 ± 0.10 (3)
7b	H	CO	H	H	β-py	H	Cl	233	2-PrOH/MeOH	1.9	$C_{14}H_9ClN_2O$·$C_2H_2O_4$	(2.8 ± 0.8) × 10^{-7}	0.68 ± 0.09 (5)
7c	H	CO	H	H	γ-py	H	Cl	260	2-PrOH/MeOH	1.7	$C_{14}H_9ClN_2O$·$C_2H_2O_4$	(3.8 ± 0.9) × 10^{-7}	0.78 ± 0.02 (3)
11a	H	CO	H	CH_3	α-py	H	OCH_3	212	EtOH/H_2O	4.5	$C_{16}H_{14}N_2O_2$·$C_2H_2O_4$·H_2O	(4.85 ± 0.6) × 10^{-6}	0.74 ± 0.07 (2)
11b	H	CO	H	CH_3	β-py	H	OCH_3	196	EtOH/H_2O	1.1	$C_{16}H_{14}N_2O_2$·HCl·0.5H_2O	(1.6 ± 0.5) × 10^{-5}	0.81 ± 0.11 (2)
11c	H	CO	H	CH_3	γ-py	H	OCH_3	245	EtOH/DMF	0.34	$C_{16}H_{14}N_2O_2$·$C_2H_2O_4$	(7.0 ± 3.0) × 10^{-6}	0.50 ± 0.22 (2)
16a	H	CO	dihydro		α-py	H	OCH_3	118	2-PrOH/MeOH	3.2	$C_{15}H_{14}N_2O_2$·HCl	(6.4 ± 2.4) × 10^{-6}	0.71 ± 0.02 (3)
16b	H	CO	dihydro		β-py	H	OCH_3	173	2-PrOH/MeOH	0.95	$C_{15}H_{14}N_2O_2$·HCl	(3.4 ± 1.8) × 10^{-5}	0.68 ± 0.11 (4)
16c	H	CO	dihydro		γ-py	H	OCH_3	~230 (168)	EtOH/H_2O	1.1	$C_{15}H_{14}N_2O_2$·HCl·H_2O	(6.5 ± 1.0) × 10^{-6}	0.68 ± 0.13 (2)
17a	H	CO	dihydro		α-py	H	H	(212)	EtOH/H_2O	1.2	$C_{14}H_{12}N_2O$·HCl	(2.55 ± 0.85) × 10^{-6}	0.29 ± 0.01 (2)
17b	H	CO	dihydro		β-py	H	H	~190 (189)	EtOH/H_2O	0.32	$C_{14}H_{12}N_2O$·HCl	(1.3 ± 0.4) × 10^{-6}	0.67 ± 0.02 (4)
17c	H	CO	dihydro		γ-py	H	H	268 (268)	EtOH/MeOH	0.52	$C_{14}H_{12}N_2O$·HCl·0.25H_2O	(1.4 ± 0.5) × 10^{-5}	0.56 ± 0.18 (3)
22a	H	CO	H	H	α-py	H	H	(250)		5.7	$C_{14}H_{12}N_2O$·HCl·1.5H_2O	(1.5 ± 0.2) × 10^{-5}	0.67 ± 0.08 (2)
22b	H	CO	H	H	β-py	H	H	262	EtOH/H_2O/Et_2O	3.6	$C_{14}H_{10}N_2O$·HCl	(5.2 ± 1.8) × 10^{-7}	0.67 ± 0.02 (19)
22c	H	CO	H	H	γ-py	H	H		MeOH	0.24	$C_{14}H_{10}N_2O$·$C_2H_2O_4$·H_2O	(2.5 ± 0.5) × 10^{-6}	0.45 ± 0.02 (2)
23a	H	CO	H	H	H	α-py	H	232	MeCN	0.8	$C_{14}H_{10}N_2O$·0.5$C_4H_4O_4$·0.25H_2O	not tested	
23b	H	CO	H	H	H	β-py	H	(246)	EtOH/H_2O	3.3	$C_{14}H_{10}N_2O$·HCl·0.25H_2O	(8.3 ± 0.81) × 10^{-6}	0.67 ± 0.16 (3)
24b	H	CO	H	H	H	H	β-py	207	EtOH/MeOH	5.5	$C_{14}H_{10}N_2O$·HCl	(1.4 ± 0.9) × 10^{-4}	0.41 ± 0.11 (3)
25	H	CO	H	H	β-COI[e]	H	H	220–250	EtOAc/MeOH	5	$C_{17}H_{16}N_2O$·HCl·H_2O	(1.05 ± 0.5) × 10^{-6}	0.38 ± 0.01 (4)
33a	H	CO	H	H	α-py	H	OCH_3	(152)	MeCN/MeOH	1.3	$C_{15}H_{12}N_2O_2$·HCl·0.5H_2O	(9.2 ± 4.2) × 10^{-6}	0.72 ± 0.06 (6)

33b	H	CO	H	H	β-py	H	OCH_3	(200)	2-PrOH/MeOH	1.96	$C_{15}H_{12}N_2O_2 \cdot C_2H_2O_4$	$(6.5 \pm 3.3) \times 10^{-6}$	0.57 ± 0.06 (3)
33c	H	CO	H	H	γ-py	H	OCH_3	268	EtOH/H_2O	0.55	$C_{15}H_{12}N_2O_2 \cdot HCl \cdot H_2O$	$(5.0 \pm 1.0) \times 10^{-6}$	0.88 ± 0.06 (3)
34a	H	CO	H	H	α-py	H	OH	244	EtOH/H_2O	1.1	$C_{14}H_{10}N_2O_2 \cdot HCl \cdot 0.75H_2O$	$(1.9 \pm 0.6) \times 10^{-5}$	0.51 ± 0.15 (2)
34b	H	CO	H	H	β-py	H	OH	(143)	EtOH/H_2O	1.37	$C_{14}H_{10}N_2O_2 \cdot HCl$	$(7.5 \pm 4.4) \times 10^{-7}$	0.72 ± 0.05 (2)
35	MOE[f]	CO	H	H	β-py	H	H	(150)	EtOH/H_2O	3.0	$C_{20}H_{21}N_3O_2 \cdot 2HCl \cdot H_2O$	$(2.2 \pm 0.15) \times 10^{-5}$	0.58 ± 0.08 (2)
36	H	*O*-MOE	H	H	β-py	H	H	(87)	MeCN/MeOH	1.0	$C_{20}H_{21}N_3O_2 \cdot 1.5C_2H_2O_4$	$(1.5 \pm 0.5) \times 10^{-5}$	0.23 ± 0.08 (4)
37	CH_3	CO	H	H	β-py	H	H	(146)	MeCN/MeOH	1.4	$C_{15}H_{12}N_2O \cdot C_2H_2O_4 \cdot 1.5H_2O$	$(1.1 \pm 0.2) \times 10^{-4}$	0.33 ± 0.13 (4)
ARL 115												$(1.2 \pm 0.3) \times 10^{-5}$	0.85 ± 0.05 (4)
milrinone												$(1.4 \pm 0.6) \times 10^{-5}$	0.67 ± 0.06 (3)
isoprenaline												$(1.5 \pm 0.1) \times 10^{-9}$	1.0 (32)

[a] In parentheses, melting point of the base. [b] Overall yield from the initial commercial aniline. [c] All compounds were analyzed for C, H, and N and gave results within ±0.4% of the theoretical values. [d] Intrinsic activity was calculated as the ratio of the maximum response to each compound to the maximum response to isoprenaline (isoprenaline: 1). Number of experiments in parentheses. [e] 2,4,6-Trimethylpyridine. [f] MOE = morpholinoethyl.

which was rechromatographed on a silica gel column with $CHCl_3$/EtOAc/MeOH (40:50:10) to give pure **11b** (3%) and **11c** (0.9%).

3,4-Dihydro-8-methoxy-2-quinolone (13). A solution of **12**[19] (21 g, 120 mmol) in EtOH (200 mL) containing 5% Rh/Al_2O_3 (1.7 g) and $HClO_4$ (2 mL) was reduced (15 kg, 50 °C) in a steel bomb for 6 h. After cooling, the catalyst was filtered and the solution concentrated to ca. 100 mL under reduced pressure. The solution was diluted with water (100 mL), made alkaline with 10% $NaHCO_3$ (50 mL), and extracted with $CHCl_3$. The $CHCl_3$ was dried ($MgSO_4$) and evaporated to give a residue that was chromatographed on silica gel (350 g). A mixture of EtOAc/$CHCl_3$ (8:2) eluted **13** as white crystals: yield 16.7 g (79%); mp 98 °C (i-Pr_2O). Anal. ($C_{10}H_{11}NO_2$) C, H, N.

8-Methoxy-6-nitro-3,4-dihydroquinolone (14). To an ice-cooled solution of **13** (23.6 g, 133 mmol) in Ac_2O (210 mL) was added dropwise a solution of HNO_3 (9.25 mL, d = 1.4) in AcOH (70 mL) during ca. 0.5 h. TLC indicated that the reaction was incomplete, so HNO_3 (1.8 mL) was added. After 1 h, the reaction appeared to be complete. The solvents were evaporated under reduced pressure, and the residue was triturated with EtOAc, filtered, and washed with a minimum of Et_2O to give practically pure **14**: yield 25.3 g (86%); mp 222 °C (MeOH). Anal. ($C_{10}H_{10}N_2O_4$) C, H, N.

8-Methoxy-6-amino-3,4-dihydroquinolone (15). A mixture of **14** (25.3 g) in EtOH (500 mL) containing PtO_2 (1 g) was reduced for 5 h. Monitoring the reaction by TLC ($CHCl_3$/2-PrOH (9:1)) showed some unreacted **14**. The solution was heated to 50 °C under hydrogen for a further 1 h. Filtration over Celite and evaporation gave **15**, which was triturated with a minimum of 2-PrOH and filtered: yield 17.3 g (79%); mp 153 °C (EtOAc). Anal. ($C_{10}H_{12}N_2O_2$) C, H, N.

8-Methoxy-6-pyridyl-3,4-dihydroquinolones 16a–c. Diazotization of **15** (32.8 g, 171 mmol) followed by the addition of pyridine (see preparation of **7a–c**) gave **16a–c** as a mixture of isomers. Silica gel column chromatography (500 g) with EtOAc/CH_2Cl_2/MeOH (50:45:5) eluted first **13** (3.7 g) followed by three fractions enriched in α, β, and γ isomers, respectively. Each fraction was chromatographed two to three more times on silica gel (200 g) with EtOAc/2-PrOH (95:5) to give 7 g of pure **16a** (16%), 2.1 g (4.8%) of **16b**, and 2.4 g (5.5%) of **16c**.

6-Pyridyl-3,4-dihydroquinolones 17a–c. The 8-methoxy group of **16a–c** was removed with a standard method[7] involving demethylation with refluxing in 48% HBr, mesylation with MesCl,[17] and hydrogenolysis over Pd/C. Yields and chemical data are shown in Table I.

Pyridyl-2(1*H*)-quinolone Derivatives 22a–c, 23a,b, and 24b. (2-, (3-, and (4-nitrophenyl)pyridine isomers were prepared as described previously[6] and were purified by silica gel column chromatography eluting with EtOAc/hexane (1:1). They were then reduced with $SnCl_2$/HCl, and without purification, each amino derivative was reacted with ethoxyacryloyl chloride as described by Effenberger and Hartmann[18] to give the crude amide derivatives **19b**, **20a,b**, and **21a–c**, used as such for the next step.

Compounds **19b**, **20a,b**, or **21a–c** (4.5 g, 168 mmol) were added in portions to concentrated H_2SO_4 (45 mL). After 1 h, the acidic mixture was poured into ice–water and alkalinized (K_2CO_3). The $CHCl_3$ extracts were dried ($MgSO_4$) and evaporated. The residue (2.6 g) was purified by column chromatography (silica gel, $CHCl_3$/MeOH (96:4) as eluent). Compounds **22a–c** were thus prepared from **21a–c** and compound **24b** from **19b**.

Compounds **23a** and **23b** were prepared from **20a** and **20b**. The major 7-pyridyl isomer (64%) was purified by recrystallization

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from MeOH, and the minor 5-pyridyl isomer (12%) was isolated by silica gel column chromatography with $CHCl_3$/MeOH (96.5:3.5) as eluent.

6-(2,4,6-Trimethylpyridyl)-2(1*H*)-quinolone (25). Diazotization of 4-nitroaniline followed by addition of 2,4,6-trimethylpyridine gave (4-nitrophenyl)-2,4,6-trimethylpyridine in 36% yield. Reduction of the crude nitro derivative with $SnCl_2$/HCl followed by reaction with ethoxyacryloyl chloride gave the amide **21d** (95%), which was cyclized with H_2SO_4 as above to give **25**.

2-Nitro-5-methoxyacetanilide (27) and 3-Methoxy-4-nitroacetanilide (28). Nitration of **26** in Ac_2O with HNO_3 in AcOH as described[1,16] (see preparation of 14) gave a mixture of **27** (39%) and **28** (24%), which were purified as follows. After completion of the reaction, the acidic solution was concentrated to ca. 50% and poured into excess water. The solid formed was filtered and suspended in EtOAc (ca 1 L/mol of **26**). The insoluble orange material was filtered and identified as **27**. The mother liquor was evaporated under reduced pressure and taken up in $CHCl_3$. Filtration and evaporation of the $CHCl_3$ solution gave **28**. The purification procedure was repeated, with yields being as indicated and ca. 15% of a mixture of **27** and **28**.

27: mp 127 °C (lit.[8] mp 125 °C); NMR (acetone-d_6) δ 1.65 (3 H, CH_3, s), 3.40 (3 H, CH_3O, s), 6.63 (1 H, dd, Ar H, J = 9 Hz, $J \cong 2$ Hz), 7.25 (1 H, d, Ar H, J = 2 Hz), 7.32 (1 H, d, Ar H, J = 9 Hz).

28: mp 167 °C (lit.[8] mp 165 °C); NMR (acetone-d_6) δ 2.28 (3 H, CH_3, s), 3.88 (3 H, CH_3O, s), 6.60 (1 H, dd, Ar H, J = 9 Hz, J = 2 Hz), 8.13 (1 H, d, Ar H, J = 9 Hz), 8.33 (1 H, d, Ar H, J = 2 Hz).

3-Methoxy-4-nitroaniline (29). A solution of **28** (25.2 g, 120 mmol) in water (665 mL) and HCl (35 mL) was heated under reflux for 4 h (monitored by TLC). The solution was diluted with water (500 mL), alkalinized (K_2CO_3), and extracted with $CHCl_3$ to give **29**: 89%; mp 160 °C (lit.[8] mp 169 °C).

8-Hydroxy- and 8-Methoxy-6-pyridyl-2-quinolones 33a–c and 34a,b. These compounds were prepared from **29** following the synthesis route adopted for **7a–c** in Scheme IV. Demethylation was performed by refluxing in 48% HBr.

***N*-(2-Morpholinoethyl)-6-β-pyridyl-2-quinolone (35) and *O*-(2-Morpholinoethyl)-6-β-pyridyl-2-quinoline (36).** NaH (0.864 g, 18 mmol) was added slowly to a solution of **22b** (3.99 g, 18 mmol) in hot DMF (18 mL). The solution was stirred magnetically until no hydrogen was given off. To the sodium salt of the quinolone thus produced was then added a solution of 2-morpholinoethyl chloride hydrochloride (3.33 g, 18 mmol) in DMF (18 mL) containing NaH (0.864 g, 50% in mineral oil, 18 mmol), and the mixture was stirred for 12 h at 60 °C. Then, water was added, and the mixture was extracted with $CHCl_3$, dried ($MgSO_4$), filtered, and evaporated under reduced pressure. The crude residue (ca. 6 g) was chromatographed on a silica gel column (200 g) with EtOAc/MeOH (9:1) as eluent to give **36** (1 g, 17%) followed by **35** (2.8 g, 46%). **35**: IR ($CHCl_3$) ν(CO) 1650 cm^{-1}. **36** IR absence of a CO bond.

***N*-Methyl-6-β-pyridyl-2-quinolone (37).** This was prepared from **22b** as described for **35** except that dimethyl sulfate was used as an alkylating agent.

Pharmacology. Isolated Left Guinea Pig Atria. Guinea pigs of either sex, in a weight range of 300–800 g, were pretreated with reserpine (5 mg/kg, ip) 24 h before death. Positive inotropism was measured on isolated left atria, according to Horii et al.[13] Left atria were stimulated electrically with a square-wave pulse stimulator at a frequency of 2.5 Hz and a voltage 50% above the threshold (duration 5 ms). The atria was suspended in Krebs–Henseleit solution, aerated with 95% O_2 and 5% CO_2, at a temperature of 32 °C, and stretched to a resting tension of 0.5 g. The physiological solution (mM) consisted of the following: NaCl, 120; KCl, 4.80; $MgSO_4 \cdot 7H_2O$, 1.20; $CaCl_2 \cdot 2H_2O$, 2.53; KH_2PO_4, 1.20; $NaHCO_3$, 25; glucose, 10. The bath fluid contained phentolamine, 3.15×10^{-4} mM. Before the construction of dose–response curves for each cardiotonic agent, an isoprenaline dose–response curve was established to test the preparation. ED_{50} values (mol·L^{-1}) were determined with the method of Ariens and Van Rossum[14] (ED_{50} = dose that produces 50% of the maximum effect). Intrinsic activity was expressed as the ratio of the maximum response to each compound to the maximum response to isoprenaline.[15] The sample size for each experiment is given in parentheses. Milrinone [1,6-dihydro-2-methyl-6-oxo-3,4′-bipyridine-5-carbonitrile hydrochloride; Sterling-Winthrop Research Institute], ARL-115 [Sulmazole, 2-[2-methoxy-4-(methylsulfinyl)phenyl]-1*H*-imidazo[4,5-*b*]pyridine; K. Thomae, GmBH, Biberach, FRG], and isoproterenol [Fluka AG, CH-9470 Buchs, Switzerland] were used as reference molecules.

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Registry No. 1, 95-51-2; **2**, 73108-79-9; **3**, 23981-25-1; **4**, 103347-84-8; **5**, 103347-85-9; **5**·HCl, 103348-22-7; **7a**, 103347-98-4; **7a**·oxalate, 103348-23-8; **7b**, 103347-99-5; **7b**·oxalate, 103348-24-9; **7c**, 103348-00-1; **7c**·oxalate, 103348-25-0; **8**, 30198-01-7; **9**, 50553-66-7; **10**, 50553-65-6; **11a**, 103348-01-2; **11a**·oxalate, 103348-26-1; **11b**, 103348-02-3; **11b**·HCl, 103348-27-2; **11c**, 103348-03-4; **11c**·oxalate, 103348-28-3; **12**, 22614-69-3; **13**, 53899-19-7; **14**, 71280-12-1; **15**, 71280-13-2; **16a**, 103348-04-5; **16a**·HCl, 103348-29-4; **16b**, 103348-05-6; **16b**·HCl, 103348-30-7; **16c**, 103348-06-7; **16c**·HCl, 103348-31-8; **17a**, 103348-07-8; **17a**·HCl, 103348-32-9; **17b**, 99471-41-7; **17b**·HCl, 103348-33-0; **17c**, 99471-42-8; **17c**·HCl, 103348-34-1; **19b**, 103347-87-1; **20a**, 103348-08-9; **20b**, 103348-09-0; **21a**, 103348-10-3; **21b**, 103348-11-4; **21c**, 103348-12-5; **21d**, 103348-13-6; **22a**, 99470-75-4; **22a**·HCl, 103348-35-2; **22b**, 99470-74-3; **22b**·HCl, 99455-04-6; **22c**, 99470-76-5; **22c**·oxalate, 103348-36-3; **23a**, 99470-98-1; **23a**·$C_4H_4O_4$, 103348-37-4; **23b**, 99470-99-2; **23b**·HCl, 103348-38-5; **24b**, 103347-89-3; **24b**·HCl, 103348-39-6; **25**, 103347-90-6; **25**·HCl, 103348-40-9; **26**, 588-16-9; **27**, 20628-18-6; **28**, 20628-19-7; **29**, 16292-88-9; **30a**, 103347-91-7; **30b**, 103347-92-8; **30c**, 103347-93-9; **31a**, 103347-94-0; **31b**, 103347-95-1; **31c**, 103348-14-7; **32a**, 103348-15-8; **32b**, 103348-16-9; **32c**, 103348-17-0; **33a**, 103348-18-1; **33a**·HCl, 103348-41-0; **33b**, 103348-19-2; **33b**·oxalate, 103348-42-1; **33c**, 103348-20-5; **33c**·HCl, 103348-43-2; **34a**, 103347-86-0; **34a**·HCl, 103348-44-3; **34b**, 103347-88-2; **34b**·HCl, 103348-45-4; **35**, 103347-96-2; **35**·2HCl, 103348-46-5; **36**, 103347-97-3; **36**·oxalate, 103348-47-6; **37**, 99471-47-3; **37**·oxalate, 103348-48-7; cinnamoyl chloride, 102-92-1; ethoxyacryloyl chloride, 6191-99-7; 4-nitroaniline, 100-01-6; 2,4,6-trimethylpyridine, 108-75-8; morpholinoethyl chloride hydrochloride, 3647-69-6; dimethyl sulfate, 77-78-1; 3-(2-nitrophenyl)pyridine, 4253-80-9; 2-(3-nitrophenyl)pyridine, 4253-79-6; 3-(3-nitrophenyl)pyridine, 4282-50-2; 2-(4-nitrophenyl)pyridine, 4282-47-7; 3-(4-nitrophenyl)pyridine, 4282-46-6; 4-(4-nitrophenyl)pyridine, 4282-45-5; 2,4,6-trimethyl-3-(4-nitrophenyl)-pyridine, 103348-21-6.