Articles

Cardiotonic Agents. 1. Synthesis and Structure–Activity Relationships in a New Class of 3-, 4-, and 5-Pyridyl-2(1*H*)-quinolone Derivatives

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A series of 3-, 4-, and 5-pyridyl-2(1*H*)-quinolone derivatives with H or HO or CH_3O substituents in the 8-position were prepared and tested for positive inotropic activity. Several derivatives, especially **29**, **9b**, and **27** with a pyridyl ring in the 5-position, were ca. 2–10 times more potent on left guinea pig atria than sulmazole (ARL-115) and milrinone used as references. Some structure–activity relationships are discussed.

At present, two classes of inotropic agents are available for treating congestive heart failure: the cardiac glycosides (digoxin and digitoxin) and the sympathomimetic agents (dobutamine and dopamine).[1,2] The use of the latter is limited by their chronotropic liability and oral ineffectiveness. The cardiac glycosides act orally, but their use is limited by their arrhythmogenic liability.[3] In recent years, much research in the field of nonsteroid cardiotonics[4] has been devoted to the quest for a safe and orally active compound.

Recently,[5] we have been looking for a pharmacophoric pattern among various cardiotonic agents including amrinone, milrinone, sulmazole (ARL-115), RMI 82249, piroximone, CI 914, and RO-136438 (Scheme I). This study, based on computer modelling (SYBYL), indicates that positive inotropic action would basically require an aromatic hydrophobic area and an electronegative region produced by an amide system that could have a tautomeric form at ca. 5 Å from the aromatic center and at a height of 0.5–0.9 Å from its plane (Figure 1). We thought the combination of an amide-containing compound, such as the carbostyril nucleus, with a pyridyl ring might give rise to new positive inotropic agents. With this in mind, we prepared 3-, 4-, and 5-pyridyl-2(1*H*)-quinolone derivatives to investigate their biological activities.[6] The very recent disclosure of a patent from Pfizer[7] has now prompted us to report our results.

Chemistry

Physicochemical data of compounds studied are shown in Tables I and II. Compounds with a pyridyl nucleus in the 4-position were prepared by heating *o*-methoxyisonicotinoylacetanilide[8] (1) with polyphosphoric acid. Demethylation of the resulting 4-γ-pyridylquinolone **2** with 48% HBr gave the corresponding 8-OH derivative **3** (Scheme II).

Most of the 5-pyridylquinolone derivatives were prepared as shown in Scheme III. The action of diazotized *p*-anisidine on pyridine, as described by Haworth et al.,[9] gave a mixture of anisoylpyridines **4a–c**, which were most conveniently separated by silica gel column chromatography. Nitration of each (methoxyphenyl)pyridine gave a single product shown to be (3-nitro-4-methoxyphenyl)-pyridine **5a–c**.[9,10] This was followed by $SnCl_2$ reduction[11] to give 5-pyridyl-2-methoxyanilines **6a–c**.[12] The method of Effenberger and Hartmann,[13] with 3-ethoxyacryloyl chloride, was used to prepare *N*-(3-ethoxyacryloyl)-5-pyridyl-*o*-anilidines **7a–c**. Cyclization of **7b–c** with H_2SO_4 gave **9b** and **9c**. Other acid catalysts, such as concentrated hydrochloric acid, acetic acid, or a mixture of phosphoric acid and phosphoric pentoxide, were either unsuccessful or led to the methoxyaniline derivatives **6b–c**, as did heating. Unexpectedly, the α-(3-amino-4-methoxyphenyl)pyridine **6a** failed to cyclize into the corresponding quinolone **9a**, which was finally prepared by adding diazotized **22** (Scheme V) to pyridine.

Similarly, acylation of **6b** with 2-ethoxypropene[14] gave the corresponding anilide **8b**. This compound could not, however, be cyclized into **10b** as before, probably because of steric hindrance between the 5-pyridyl and 4-methyl substituents. The only product that could be isolated by acidic treatment of **8b** was the acetylacetamido derivative **11b**. This compound, also easily obtained by reacting **6b** and diketene, failed to cyclize to **10b** under a variety of thermal and acidic conditions. Since the ring-closure route did not work, we tried introducing the pyridyl nucleus on the 4-methylquinolone **14**, as described in Scheme IV. Condensation of diketene with *o*-anisidine (**12**) gave 2-methoxyacetoacetanilide **13** with a 94% yield.[15] Cyclization with polyphosphoric acid gave 8-methoxy-4-methyl-2(1*H*)-quinolone (**14**) (80% yield), which was followed by nitration in acetic anhydride,[16] giving a mixture

† Département de Pharmacochimie.

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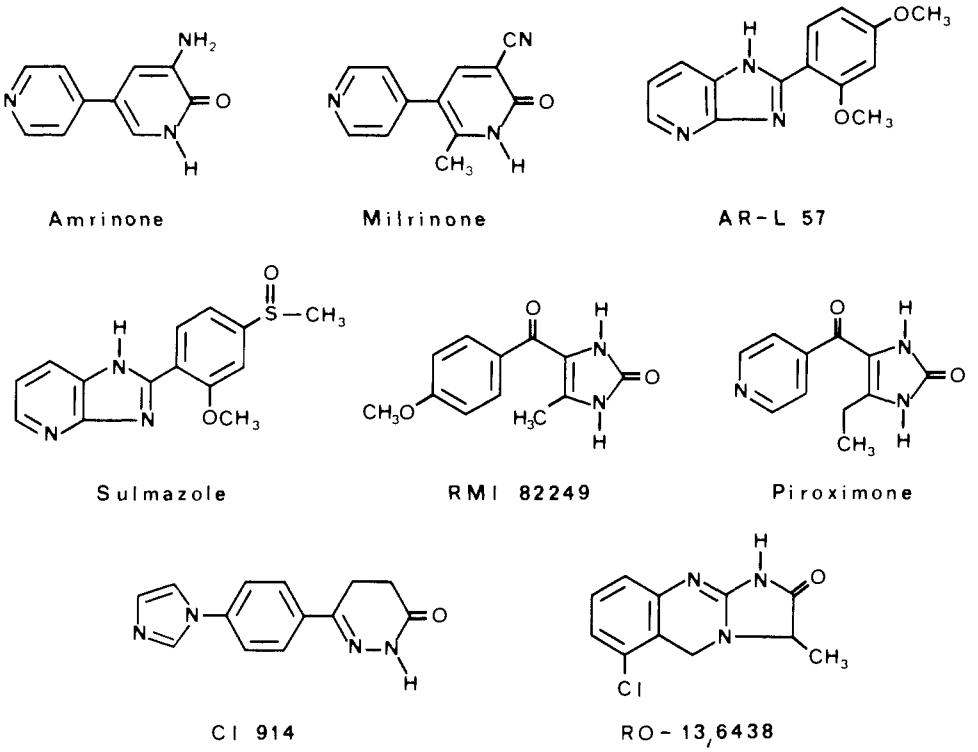
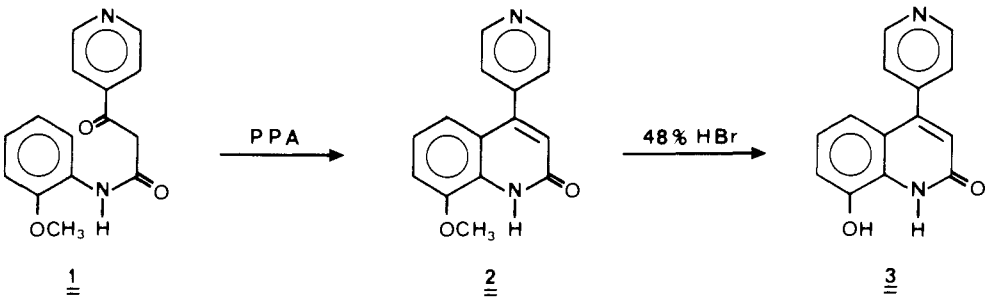
Scheme I. Structures of Nonsteroid Cardiotonic Agents



Scheme II. Synthesis of 4-Pyridyl-2(1*H*)-quinolones **2** and **3**



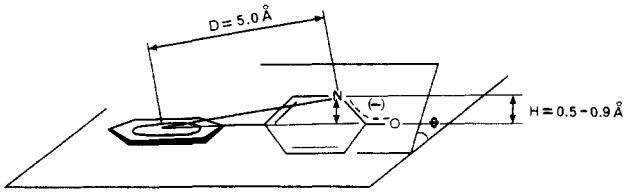


Figure 1. Pharmacophoric requirements of the nonsteroid cardiotonic agents (ref 5).

of **15** (48%) and **16** (30%). Compound **15** was easily identified from its NMR spectra, which revealed two low-field doublets (δ 7.82 and 8.15) with a coupling constant of ca. 2 Hz, characteristic of the meta protons. Catalytic hydrogenation of the 5-nitro derivative **16** led to amine **17**, which was diazotized and added to pyridine, as previously described. The reaction was shown to follow a different course, giving mainly quinolone **14** (33%) mixed with minute amounts (<5%) of the expected pyridylquinolones **18a**, **18b**, and **18c**. It is not clear how **14** is formed by reduction of the diazonium group, although it probably involves free-radical species.[17] The steric hindrance of the 4-methyl group prevents the normal coupling reaction, thus favoring dediazonation, presumably by removing a hydrogen radical from pyridine.

Dihydroquinolone compounds could not be obtained from **9a–c** (Scheme III) since catalytic hydrogenation (Rh/Al_2O_3, 15 atm) conditions gave the corresponding piperidine derivatives by reduction of the pyridyl nucleus. We therefore adopted the route indicated in Scheme V using 8-methoxycarbostyril **19** as the starting point. Nitration of **19** in Ac_2O/AcOH, between 0 and 5 °C, gave a roughly equal mixture of **20** and **21**. We thus confirmed the detrimental steric effect of the 4-methyl group on the preparation of 5-NO_2 derivatives. We took advantage of the greater solubility of **20** in MeCN and of its poorer solubility in AcOH to isolate it, with a yield of about 40%. The 5-nitro-8-methoxyquinolone **20** was easily identified by its NMR spectra, in which the aromatic protons appeared as two-field doublets (δ 7.35 and 8.10) with a coupling constant J = 7.5 Hz. The structure of **20** was confirmed by the appearance in isomer **21** of two doublets at δ 7.85 and 8.45 with a coupling constant $J \sim 2$ Hz, characteristics of the meta protons, H_5 and H_7. The amount of the 6-nitro derivative **21** was unexpected and presumably resulted from the activating effect of the quinolone amide group on electrophilic substitution in the 6-position. Nitration of 8-methoxy-3,4-dihydroquinolone gave only the 6-nitro isomer,[18] which indicates that the 8-OCH_3 group has a poor para-orienting effect. Hydrogenation of **20** with

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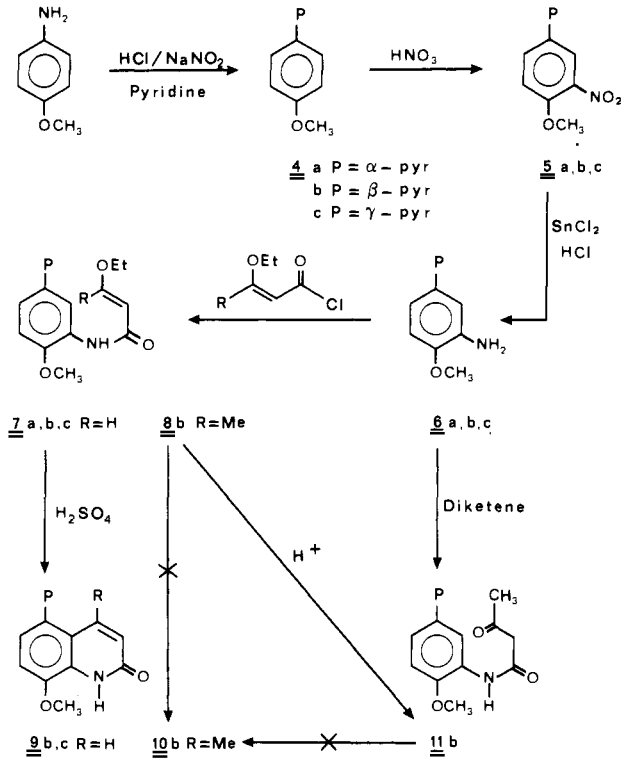
Scheme III. Synthesis of 5-Pyridyl-2(1*H*)-quinolones **9b,c**[a]



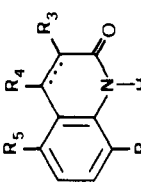
[a] For **9a** see text. pyr = pyridine.

PtO_2 at room temperature, followed by hydrogenation of the resulting **22** with Rh/Al_2O_3, at 50 °C and 15 atm, produced **23**, which was diazotized and added to pyridine to give a mixture of **24a** (5%), **24b** (3.2%), and **24c** (3%) isomers.

Adding 3-quinolone diazonium salts to pyridine gave very low yields of 3-pyridyl derivatives. So, we prepared compound **26** by a coupling reaction between 3-bromo-2-(1*H*)-quinolone (**25**) and pyridylzinc chloride (Scheme VI). Pyridylzinc chloride was most conveniently obtained in situ by reacting the 3-chloropyridine in THF at −75 °C, with 2 equiv of BuLi to obtain the lithio derivative, which was then reacted with a solution of anhydrous $ZnCl_2$ in THF. The final 3-pyridylquinolone **26** was obtained by adding the 3-bromoquinolone **25** to the mixture in the presence of tetrakis(triphenylphosphine)palladium as a catalyst. Compound **25** was prepared with a 35% yield, from commercial 3-bromoquinoline, via its *N*-oxide.[19,20]

The compound unsubstituted in the 8-position, **29**, was prepared from the corresponding 8-OCH_3 derivative **9b** with the method of Clauss and Jensen.[21] Demethylation of the 8-OCH_3 derivatives **9b** and **9c** with 48% HBr gave the corresponding 8-OH derivatives **27** and **28**. Compound **27** was mesylated and submitted to catalytic reduction over Pd/C to give **29**. We did not succeed in preparing 8-chloro-5-pyridylquinolone by the cyclization reaction of **31** in the same manner as described in Scheme III, which indicates the highly detrimental effect of the electronegative chlorine atom in this position. Furthermore, nitration of 8-chloro-2(1*H*)-quinolone gave solely the 6-NO_2 derivative,[18] as the NMR spectra revealed, which provides evidence for the strong meta-orienting effect of the chlorine atom, in addition to the para-activating effect of the quinolone amide group.

Table I. Physicochemical Data and in Vitro Positive Inotropic Activities of Pyridyl- and Aminoquinolone

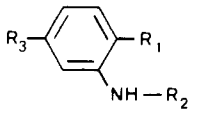


no.	R_3	R_4	R_5	R_8	mp, °C	crystn solvent	yield,[a] %	empirical formula	anal.	inotropic activity: ED_{50} ± SEM, M	inotropic activity: intrinsic act.[b] ± SEM (*n*)
2	H	γ-pyr[c]	H	OCH_3	226	EtOH/H_2O	16	$C_{15}H_{12}N_2O_2{\cdot}HCl{\cdot}0.5H_2O$	C, H, N	$(3.8 \pm 2.2)10^{-5}$	0.45 ± 0.08 (2)
3	H	γ-pyr	H	OH	>260	EtOH/H_2O	8	$C_{14}H_{10}N_2O_2{\cdot}HCl{\cdot}0.75H_2O$	C, H, N	$(2.2 \pm 0.35)10^{-5}$	0.55 ± 0.05 (2)
9a	H	H	α-pyr	OCH_3	200	MeCN/MeOH	9	$C_{15}H_{12}N_2O_2{\cdot}C_2H_2O_4$	C, H, N	$(3.45 \pm 1.3)10^{-6}$	0.62 ± 0.02 (2)
9b	H	H	β-pyr	OCH_3	191	EtOH/H_2O	7	$C_{15}H_{12}N_2O_2{\cdot}HCl$	C, H, N	$(5.75 \pm 1.8)10^{-6}$	0.79 ± 0.11 (2)
9c	H	H	γ-pyr	OCH_3	258	EtOH/H_2O	5.3	$C_{15}H_{12}N_2O_2{\cdot}HCl{\cdot}0.75H_2O$	C, H, N	$(3.5 \pm 2.0)10^{-5}$	0.75 ± 0.03 (5)
22	H	H	NH_2	OCH_3	202	EtOH	9.2	$C_{10}H_{10}N_2O_2{\cdot}HCl{\cdot}0.75H_2O$	C, H, N	$(2.35 \pm 0.64)10^{-4}$	0.23 ± 0.05 (2)
24a	3,4-dihydro		α-pyr	OCH_3	190	MeCN	0.7	$C_{15}H_{14}N_2O_2{\cdot}C_2H_2O_4$	C, H, N	$(2.2 \pm 1.7)10^{-5}$	0.44 ± 0.03 (3)
24b	3,4-dihydro		β-pyr	OCH_3	166	EtOH	0.4	$C_{15}H_{14}N_2O_2{\cdot}HNO_3$	C, H, N	$(1.2 \pm 0.2)10^{-5}$	0.56 ± 0.08 (5)
24c	3,4-dihydro		γ-pyr	OCH_3	215	2-PrOH/MeOH	0.4	$C_{15}H_{14}N_2O_2{\cdot}C_2H_2O_4$	C, H, N	$(3.1 \pm 1.1)10^{-5}$	0.75 ± 0.08 (6)
26	β-pyr	H	H	H	246	2-PrOH/MeOH	0.8[c]	$C_{11}H_{10}N_2O{\cdot}C_2H_2O_4{\cdot}0.5H_2O$	C, H, N	3×10^{-4}[d]	0.08 ± 0.11 (2)
27	H	H	β-pyr	OH	>260	EtOH/H_2O	4.6	$C_{14}H_{10}N_2O_2{\cdot}HBr$	C, H, N	$(6.75 \pm 2.75)10^{-6}$	0.62 ± 0.07 (2)
28	H	H	γ-pyr	OH	>260	EtOH/H_2O	3.1	$C_{14}H_{10}N_2O_2{\cdot}HCl{\cdot}0.25H_2O$	C, H, N	2×10^{-5}[d]	0.24 ± 0.06 (2)
29	H	H	H	H	252	EtOH/MeOH	1	$C_{14}H_{10}N_2O{\cdot}C_4H_4O_4$	C, H, N	$(1.3 \pm 0.8)10^{-6}$	0.83 ± 0.01 (2)
30	NH_2	H	H	H	211	AcOEt/MeOH	2.5	$C_9H_{10}N_2O{\cdot}HCl$	C, H, N	$>7.7 \times 10^{-5}$	0.20 ± 0.14 (3)

[a] Overall yield from the starting aniline, except for **9a**, **24a**, **24b**, and **24c** prepared from 8-methoxy-2(1*H*)-quinolone. [b] 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. [c] Yield from commerical 3-bromoquinoline. [d] Dose that gives maximum intrinsic activity. [e] pyr is pyridyl.

(19) Pettit, G. R.; Kalnins, M. *J. Org. Chem.* **1960**, *25*, 1365.
(20) Pettit, G. R.; Kleming, W. C.; Paull, K. D. *J. Org. Chem.* **1968**, *33*, 1089.
(21) Clauss, K.; Jensen, H. *Angew. Chem.* **1973**, *85*, 981.

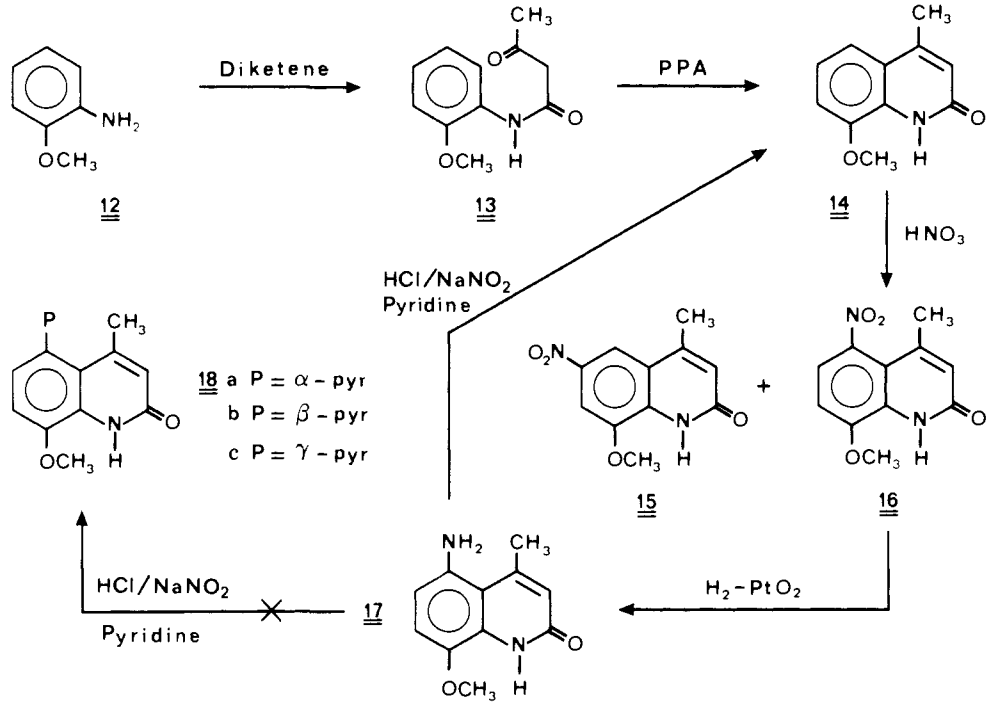
Table II. Positive Inotropic Activities of Pyridyl Anilide Intermediates, in Vitro



compd	R_1	R_2	R_3	inotropic activity: ED_{50} ± SEM, M	inotropic activity: intrinsic act.[a] ± SEM (n)
7b	OCH_3	COCH=CHOEt	β-pyr	(1.0 ± 0.50) 10^{-5}	0.54 ± 0.09 (2)
11b	OCH_3	$COCH_2COCH_3$	β-pyr	(8.3 ± 1.5) 10^{-6}	0.51 ± 0.11 (2)
31	Cl	COCH=CHOEt	β-pyr	(2.4 ± 2.15) 10^{-5}	0.28 ± 0.07 (5)
32a[b]	H	COCH=CHOEt	α-pyr	(1.85 ± 0.05) 10^{-6}	0.33 ± 0.08 (2)
32b[b]	H	COCH=CHOEt	β-pyr	(3.8 ± 2.15) 10^{-5}[c]	0.42 ± 0.08 (5)
sulmazole				(1.2 ± 0.3) 10^{-5}	0.85 ± 0.05 (4)
milrinone				(1.4 ± 0.6) 10^{-5}	0.67 ± 0.06 (3)
isoprenaline				(1.5 ± 0.1) 10^{-9}	1.0 (32)

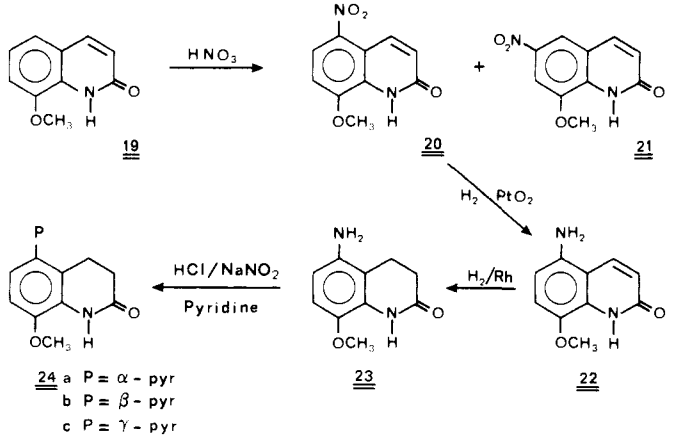
[a] Intrinsic activity was calculated as the ratio of the maximum response to each compound to the maximum response to isoprenaline; isoprenaline = 1. Number of experiments in parentheses. [b] **32a** and **32b** were prepared from *m*-nitroaniline in the same manner as described in Scheme IV. [c] Dose that gives maximum intrinsic activity.

Scheme IV. Attempted Synthesis of 4-Methyl-5-pyridyl-2(1*H*)-quinolones 18a–c[a]



[a] pyr = pyridine.

Scheme V. Synthesis of 3,4-Dihydro-5-pyridyl-2(1*H*)-quinolones 24a-c[a]



[a] pyr = pyridine.

3-Amino-2(1*H*)-quinolone (**30**) was prepared by heating the bromo derivative **25** in a steel bomb at 180 °C for 3 h with a 4:6 mixture of 33% NH_4OH and ethanol.

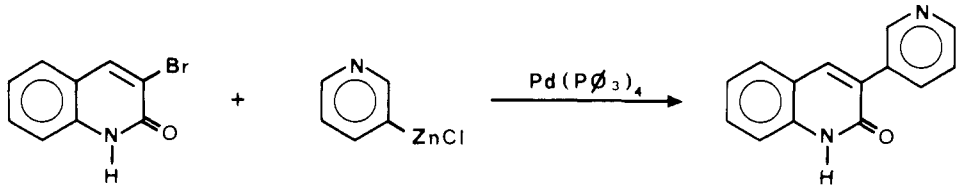
Biological Results and Discussion

Compounds were evaluated for positive inotropic activity on isolated left guinea pig atria, as described in the Experimental Section.

The dose of each compound required to produce 50% of the maximum effect is shown in Tables I and II. 5-β-Pyridylquinolone derivatives had the highest activity. Nor-substituted, 8-methoxy-substituted, and 8-hydroxy-substituted quinolone derivatives **29**, **9b**, and **27** were the most potent. Hydrogenation of the 3,4 double bond of **9b** gave **24b**, which did not offer any advantage over the starting material; its potency was half that of its homologue derivative **9b**. Compounds **9b** and **29** had the greatest intrinsic activities. Intrinsic activity was lower for compounds **24b** and **27**.

The potencies of the 5-α-pyridyl and 5-γ-pyridyl analogues **9a** and **9c** were 10 times lower than that of compound **9b**, while those of the 3,4-dihydro analogues **24a**, **24b**, and **24c** were equal, irrespective of the nitrogen position. The intrinsic activities of the γ-pyridyl deriva-

Scheme VI. Synthesis of 3-β-Pyridyl-2(1*H*)-quinolone **26**



25 **26**

tives **9c** and **24c** were higher than those of the α-pyridyl analogues **9a** and **24a**.

The 4-γ-pyridyl substitution of the quinolone ring (**2**, **3**) gave lower intrinsic activity than the parent 5-γ-pyridylquinolone **9c**, except for **3**, which was ca. 2 times more potent than **28**, but retained the same activity.

The activity vanished for compound **26** with the β-pyridyl nucleus in the 3-position.

Loss in activity was also observed when the pyridyl nucleus was replaced with an amino group in the 3- or the 5-position (**22** and **30**). This indicates that the pyridyl nucleus is important for significant positive inotropic activity.

Potencies but especially the activities of all intermediate anilide derivatives were generally lower than those of the corresponding quinolones (Table II). Table II also shows, for the sake of comparison, the inotropic responses of sulmazole[25] and milrinone.[26] Our data showed that compounds **29**, **9b**, and **27** were more potent than sulmazole and milrinone, whereas the activities of the other derivatives were identical with those of sulmazole and milrinone. The highest activities, equivalent to those of sulmazole, were observed for compounds **29**, **9b**, **9c**, and **24c**.

In conclusion, the pyridyl ring in the 4- or 5-position on the carbostyril nucleus promotes significant positive inotropic activity. The 5-pyridylquinolone derivatives were more potent positive inotropic agents than the 4-pyridyl analogues **2** and **3**, themselves more potent than the 3-pyridyl analogue **26**. The β-nitrogen position appears to promote the best potency as Robertson et al.[27] suggested for arylimidazopyridine cardiotonics. These results show that 5-β-pyridylquinolone derivatives are a new class of potent positive inotropic agents. Further detailed in vivo pharmacological investigations will be published shortly.

Experimental Section

Chemistry. Melting points 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 spectra were recorded on a 60-MHz Perkin-Elmer spectrometer using Me_4Si in a capillary as an external reference.

4-γ-Pyridyl-8-methoxy-2(1*H*)-quinolone (2). The procedure of Vulfson and Kolchin[8] gave an 89% yield of **1**. Compound **1** (0.2 g, 34 mmol) was added in portions to stirred 85% polyphosphoric acid (50 mL) at 100–110 °C. After being treated at 100–110 °C for 12 h, the acidic mixture was poured into crushed ice and alkalinized with K_2CO_3 to pH 8. The aqueous solution was thoroughly extracted with $CHCl_3$, dried, and evaporated. The crude residue was chromatographed on a silica gel column and eluted with $CHCl_3$/MeOH (95:5) to give 6.6 g (77%) of **2** as a yellow solid.

4-γ-Pyridyl-8-hydroxy-2(1*H*)-quinolone (3). A solution of **2** (1.5 g, 6 mmol) was heated under reflux in 48% HBr (30 mL) for 20 h. Excess HBr was removed in vacuo, and the resulting precipitate was filtered and washed with H_2O to give 0.95 g of the 8-hydroxy derivative hydrobromide (yield 50%). The free base was obtained by dissolving the hydrobromide in water, after the addition of 1 N NaOH to pH ~9. The free base was filtered and converted to its hydrochloride salt.

Synthesis of 4a–c. Action of Diazotized *p*-Anisidines on Pyridine. The procedure of Haworth et al.[9] was followed. The crude product was conveniently separated by silica gel column chromatography with EtOAc/hexane (1:1) to give α-(4-methoxyphenyl)pyridine (**4a**; 50%), mp 50 °C (lit.[9] mp 49–50 °C); β-(4-methoxyphenyl)pyridine (**4b**; 23%), mp 60 °C; and γ-(4-methoxyphenyl)pyridine (**4c**; 16%), mp 96 °C (lit.[9] mp 95 °C).

(3-Amino-4-methoxyphenyl)pyridines 6a–c via 5a–c. Nitration of each (4-methoxyphenyl)pyridine **4a**, **4b**, and **4c** with fuming nitric acid followed by $SnCl_2$ reduction of each isomer **5a**, **5b**, and **5c** was carried out exactly as described,[10,11] to give α-(3-amino-4-methoxyphenyl)pyridine (**6a**; 89%), mp 97 °C (lit.[12] mp 98 °C); β-(3-amino-4-methoxyphenyl)pyridine (**6b**; 85%), mp 110 °C; and γ-(3-amino-4-methoxyphenyl)pyridine (**6c**; 84%), mp 181 °C.

[3-[*N*-(3-Ethoxyacryloyl)amino]-4-methoxyphenyl]pyridines 7a–c. A solution of ethoxyacryloyl chloride (3 g, 22 mmol) and Et_2O (10 mL) was added dropwise to a solution of (3-amino-4-methoxyphenyl)pyridine (4 g, 20 mmol) **6a**, **6b**, or **6c** in Et_2O (50 mL) and THF (50 mL) with stirring and cooling in ice–water. After 1 h, the reaction mixture was washed with water (100 mL), alkalinized with powdered K_2CO_3, extracted with EtOAc, dried, and evaporated to yield 4.7 g (79%) of the α-isomer **7a**, mp (base) 176 °C. Similarly, the β-isomer **7b** was prepared and purified as an oxalate, mp 148 °C, and the γ-isomer **7c** had mp (base) 142 °C (89%).

β-[3-[*N*-(3-Ethoxycrotonoyl)amino]-4-methoxyphenyl]pyridine (8b). 2-Ethoxypropene was prepared from acetoacetic ester and orthoformic ester with an 89% yield as described.[14] Following the procedure previously described gave **8b**: yield 84%, mp 146 °C.

5-Pyridyl-8-methoxy-2(1*H*)-quinolones 9b,c. The amide **7b** or **7c** (1.8 g, 6 mmol) was added in five portions to concentrated H_2SO_4 (10 mL). After 1 h, the acidic mixture was poured into ice-cold water (150 mL) and alkalinized with K_2CO_3. The $CHCl_3$ extracts were dried ($MgSO_4$) and evaporated, and the residue was purified by silica gel column chromatography with EtOAc/MeOH (9:1) as eluent. β-Isomer **9b**: yield 60%, mp 191 °C (hydrochloride). γ-Isomer **9c**: yield 52%, mp 258 °C (hydrochloride).

Attempted Cyclization of 8b. Concentrated HCl, AcOH, H_3PO_4/P_2O_5, and H_2SO_4 at ambient temperature or up to boiling point or even heated in xylene or diphenyl oxide or without solvent failed to give the expected quinolone **10b**. Acidic treatment (H_2SO_4, room temperature) gave an almost quantitative yield of **11b**.

β-(3-Acetoacetamido-4-methoxyphenyl)pyridine (11b). By following the procedure outlined by Williams and Krynitsky,[15] **11b** was obtained from **6b** with a 90% yield, mp 173 °C (hydrochloride).

8-Methoxy-4-methyl-2(1*H*)-quinolone (14). Heating anilide **13**[16] with PPA at 100 °C (higher temperatures led to o-methoxyaniline (**12**) by hydrolysis), as described,[15] gave **14**: yield 90%,

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mp 188 °C, lit.[16] mp 188–190 °C.

8-Methoxy-4-methyl-5-nitro-2(1*H*)-quinolone (16) and 8-Methoxy-4-methyl-6-nitro-2(1*H*)-quinolone (15). Nitration of 14 in Ac_2O with fuming nitric acid[16] led to **15** (48%) and **16** (30%) purified by crystallization from MeOH (**15** is less soluble). Compound **15**: mp 286 °C; NMR (Me_2SO-d_6) δ 2.45 (3 H, d, J ~ 1 Hz), 4.0 (3 H, s), 6.6 (1 H, s, large), 7.82 (1 H, d, J ~ 2 Hz), 8.15 (1 H, d, J ~ 2 Hz). Compound **16**: mp 193 °C; NMR ($CDCl_3$) δ 2.32 (3 H, d, J ~ 1 Hz), 4.02 (3 H, s), 6.62 (1 H, s, large), 6.90 (1 H, d, J = 8.5 Hz), 7.35 (1 H, d, J = 8.5 Hz).

8-Methoxy-4-methyl-5-amino-2(1*H*)-quinolone (17). A solution of **16** (12.4 g, 53 mmol) in EtOH (250 mL) containing platinum oxide (500 mg) underwent atmospheric hydrogenation. After 3.5 h, the theoretical amount of hydrogen (3.5 L) was absorbed. To prevent crystallization of the amine, $CHCl_3$ was added, the catalyst was filtered, and solvents were removed under reduced pressure to give 14 g of crude solid, which was purified by silica gel column chromatography and eluted with $CHCl_3$/MeOH (95:5). The yield was 8.78 g (80%), mp 197 °C.

Attempted Synthesis of 18a–c. An aqueous solution of the diazonium derived from **17** [11 g of **17**, 19.2 mL of concentrated HCl, 100 mL of H_2O, 3.72 g of $NaNO_2$ (54 mmol)] was added dropwise, for 1 h, to pyridine (60 mL) stirred at 70 °C. The reaction was completed by maintaining that temperature for 1.5 h. The solution was then poured into cold NH_4OH (33%) and the mixture evaporated under reduced pressure. The residue was taken up in water and extracted with $CHCl_3$, filtered over Celite, and evaporated. Recrystallization from EtOAc/MeCN gave 3.3 g (33%) of yellow-orange crystals, mp 188 °C, identified as quinolone **14**.

8-Methoxy-5-nitro-2(1*H*)-quinolone (20) and 8-Methoxy-6-nitro-2(1*H*)-quinolone (21). Nitration of **19**[28] in Ac_2O with fuming nitric acid as described previously gave **20** (ca. 40%) and **21** (ca. 40%). Compound **20**: mp 233 °C; NMR (Me_2SO-d_6) δ 4.1 (3 H, s), 6.85 (1 H, d, J = 8.5 Hz), 7.35 (1 H, d, J = 7.5 Hz), 8.10 (1 H, d, J = 7.5 Hz), 8.55 (1 H, d, J = 8.5 Hz). Compound **21**: mp 270 °C; NMR (Me_2SO-d_6) δ 4.0 (3 H, s), 6.75 (1 H, d, J = 8.5 Hz), 8.15 (1 H, d, J = 8.5 Hz), 7.85 (1 H, d, J = 2 Hz), 8.45 (1 H, d, J = 2 Hz).

8-Methoxy-5-amino-3,4-dihydro-2(1*H*)-quinolone (23). Reduction of **20** as previously described gave the amine **22** (62%), which was used without purification in the next step.

A solution of **22** (15.6 g, 82 mmol) in EtOH (150 mL) containing Rh/Al_2O_3 (1.5 g) and $HClO_4$ (2 mL) was reduced (15 atm, 50 °C) in a steel bomb for 5 h. After cooling, the catalyst was removed and the crude alkalinized mixture was chromatographed on silica gel with $CHCl_3$/AcOEt/MeOH (45:45:10) as eluent, to give 8.25 g (52%) of **23**: mp 151 °C; NMR ($CDCl_3$) δ 2.70 (4 H, m), 3.3 (2 H, s, large, exchangeable D_2O), 3.73 (3 H, s), 6.27 (1 H, d, J = 7.5 Hz), 6.58 (1 H, d, J = 7.5 Hz), 7.75 (1 H, m, exchangeable D_2O).

8-Methoxy-5-pyridyl-3,4-dihydro-2(1*H*)-quinolones 24a–c. A solution of 8-methoxy-5-amino-3,4-dihydro-2(1*H*)-quinolone (**23**) (11.7 g, 61 mmol) in a mixture of concentrated hydrochloric acid (22 mL) and water (16 mL) was diazotized at −5 to 0 °C with a solution of $NaNO_2$ (4.2 g, 61 mmol) in water (30 mL). The resulting diazonium suspension was added dropwise for 0.5 h to pyridine (62 mL) stirred at 70 °C. The mixture was heated for another hour at 70 °C until N_2 was no longer given off. The mixture was then cooled, 33% NH_4OH (30 mL) was added, and the solvents were evaporated under reduced pressure. The residue was taken up in $CHCl_3$, filtered on Celite, and evaporated. The crude mixture of isomers (20 g) was first chromatographed on silica gel (300 g) with EtOAc/MeOH (95:5) as eluent. Each enriched isomer fraction was chromatographed again on silica gel (50 g) to give 5-α-pyridyl-3,4-dihydro-8-methoxy-2(1*H*)-quinolone (**24a**) (800 mg, 5%), 5-β-isomer **24b** (500 mg, 3.2%), and 5-γ-isomer **24c** (470 mg, 3%). Analytical samples were obtained after recrystallization of the salts indicated in Table I.

5-α-Pyridyl-8-methoxy-2(1*H*)-quinolone (9a). Diazotization of aminoquinolone **22**, followed by the addition of pyridine, was carried out exactly as described for the preparation of **24a–c**, to obtain **9a**.

3-β-Pyridyl-2(1*H*)-quinolone (26). A solution of 3-chloropyridine (2.5 g, 15.8 mmol) in THF (20 mL) was stirred at −70 °C under argon while *n*-butyllithium (20 mL of a 1.6 M solution in *n*-hexane) was added. After 10 min, a solution of anhydrous zinc chloride (2.18 g) in THF (20 mL) was added, and the mixture was allowed to warm to room temperature for 1 h. A suspension of 3-bromo-2(1*H*)-quinolone (**25**)[19,20] (1.35 g, 6 mmol) and tetrakis(triphenylphosphine)palladium (60 mg) in THF (20 mL) was then added, and the mixture was treated under reflux for 72 h. Saturated NH_4Cl solution (20 mL) was added to the cooled mixture followed by a solution of ethylenediaminetetraacetic acid disodium salt (12 g) in water (200 mL). $CHCl_3$ (200 mL) and MeOH (60 mL) were added, and the mixture was warmed until all the solid material had dissolved. The phases were separated; the aqueous layer was further extracted with chloroform/MeOH, and the combined organic extracts were dried, filtered, and concentrated in vacuo to give a solid, which was chromatographed on silica gel, eluted with $CHCl_3$/MeOH (97:3), to give **26**, 30 mg (2.2%): mp 246 °C (oxalate); NMR (CH_3OD) δ 7–7.7 (5 H, m), 7.9 (1 H, s), 8.1 (1 H, dd, J = 7.5 Hz, 2 Hz), 8.45 (1 H, m), 8.78 (1 H, d, J = 2 Hz).

3-Amino-2(1*H*)-quinolone (30). A solution of **26** (3 g, 13.4 mmol) in 95% ethanol (60 mL) and 33% NH_4OH (90 mL) was heated in a steel bomb at 180 °C for 3 h. The solvent was removed, and 1 N HCl (80 mL) was added. The mixture was extracted with EtOAc. The organic layer was discarded, and the aqueous layer was basified with solid $KHCO_3$. Extraction with EtOAc, followed by drying ($MgSO_4$) and evaporation of the solvent, gave 1.1 g (51%) of the pure 3-amino derivative, as a beige solid.

β-[3-[*N*-(3-Ethoxyacryloyl)amino]-4-chlorophenyl]pyridine (31). The effect of diazotized 3-nitro-4-chloroaniline on pyridine as previously described gave the (3-nitro-4-chlorophenyl)pyridine derivatives. The β-isomer was the major product (0.5%), mp 130 °C. Reduction with $SnCl_2$ gave (3-amino-4-chlorophenyl)pyridine, which was reacted unpurified with ethoxyacryloyl chloride to give the title compound (44% yield from the β-pyridyl compound), mp (oxalate) 153 °C.

[3-[*N*-(3-Ethoxyacryloyl)amino]phenyl]pyridines 32a,b. These compounds were obtained from (3-aminophenyl)pyridine[10] as described for **7a–c**. α-Isomer **32a**: mp (oxalate) 210 °C, yield 63%. β-isomer **32b**: mp (oxalate) 100 °C, yield 74%.

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.[22] 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 atrium 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 (in 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 (mole per liter) were determined with the method of Ariens and Van Rossum[23] (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.[24] The sample size for each experiment is given in parentheses. Milrinone, 1,6-dihydro-2-methyl-6-oxo-[3,4′-dipyridine]-5-carbonitrile hydrochloride (Sterling-Winthrop Research Institute); sulmazole (ARL-115), 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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