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Studies on Positive Inotropic Agents. II.¹⁾ Synthesis of (4-Substituted 1-piperazinylcarbonyl)-2-(1*H*)- quinolinone Derivatives

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Many (1-piperazinylcarbonyl)-2(1*H*)-quinolinone derivatives were synthesized and examined for positive inotropic activity on the canine heart. Among them, 3,4-dihydro-6-[4-(3-oxo-3-phenylpropyl)-1-piperazinylcarbonyl]-2(1*H*)-quinolinone (XXIj) and 3,4-dihydro-6-[4-(4-oxo-4-phenylbutyl)-1-piperazinylcarbonyl]-2(1*H*)-quinolinone (XXII) were found to have potent activity.

Keywords—congestive heart failure; positive inotropic agent; 1,2-dihydro-2-oxoquinoline-carboxylic acid; 3,4-dihydro-6-[4-(3-oxo-3-phenylpropyl)-1-piperazinylcarbonyl]-2(1*H*)-quinolinone; 3,4-dihydro-6-[4-(4-oxo-4-phenylbutyl)-1-piperazinylcarbonyl]-2(1*H*)-quinolinone; biological activity

Introduction

We have been searching for compounds having potent positive inotropic activity with little chronotropic effect for the treatment of congestive heart failure. In the preceding paper,¹⁾ we reported the syntheses and biological activities of (1-piperazinyl)-2(1*H*)-quinolinone derivatives. Some of them showed desirable activity on the canine heart. Encouraged by these results we undertook further studies to prepare 2(1*H*)-quinolinone derivatives, and we have now synthesized many compounds which have a carbonyl group between a 2(1*H*)-quinolinone skeleton and the nitrogen atom of a piperazine ring.

Some of the compounds were found to have potent positive inotropic activity with little chronotropic effect. Herein, we report the syntheses and biological activities of 1-piperazinylcarbonyl-2(1*H*)-quinolinone derivatives.

Chemistry

The key intermediates, 1,2-dihydro-2-oxoquinolinecarboxylic acids were prepared by three different methods.

First, 1,2,3,4-tetrahydro-2-oxo-7-quinolinecarboxylic acid (IV) was synthesized through the reductive cyclization of 4-(2-methoxycarbonyl-ethyl)-2-nitrobenzoic acid (III) (Chart 1). Methyl 3-(4-chloroacetylphenyl)propionate²⁾ (II) was obtained in 77% yield by acylation of methyl hydrocinnamate (I) with chloroacetyl chloride. Reaction of II with fuming nitric acid in sulfuric acid gave III in 70% yield. Fortunately, in this nitration the chloroacetyl group was oxidized to carboxylic acid.³⁾ Hydrogenation of III over 5% palladium on charcoal in alcoholic sodium hydroxide solution, followed by treatment with hydrochloric acid, gave IV in 95% yield.

Secondly, 1,2-dihydro-2-oxo-5-quinolinecarboxylic acid (VII) was obtained through the ring closure of the β -ethoxyacryloanilide derivative (VI) (Chart 2). Treatment of *m*-aminobenzoic acid (V) with β -ethoxyacryloyl chloride⁴⁾ gave VI in 77% yield. Cyclization of

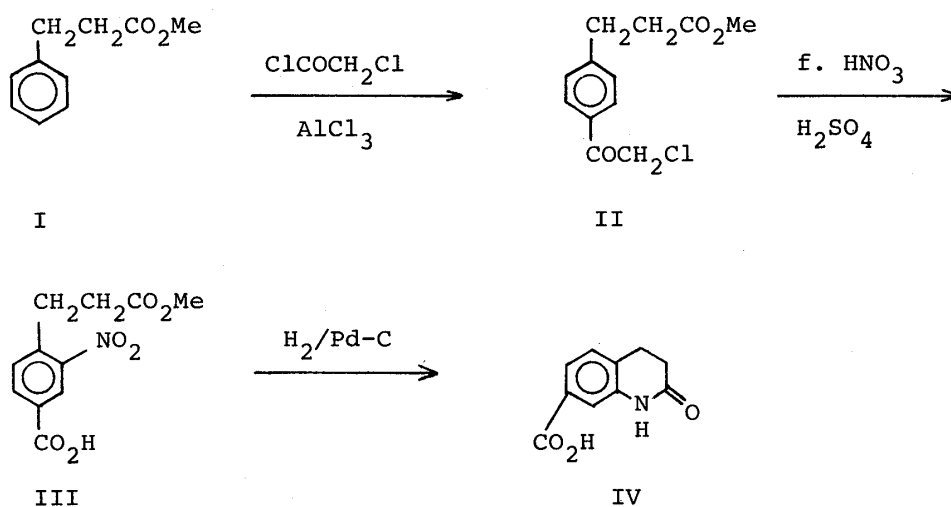


Chart 1

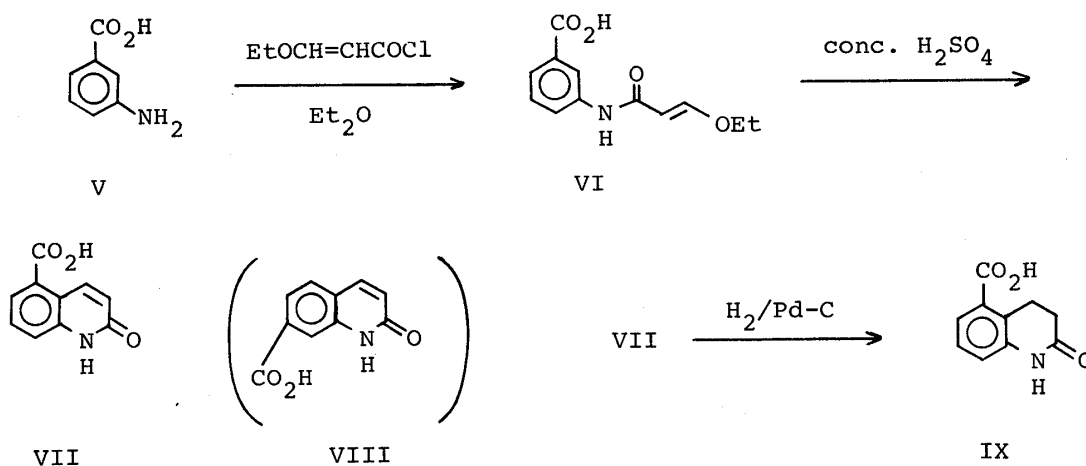


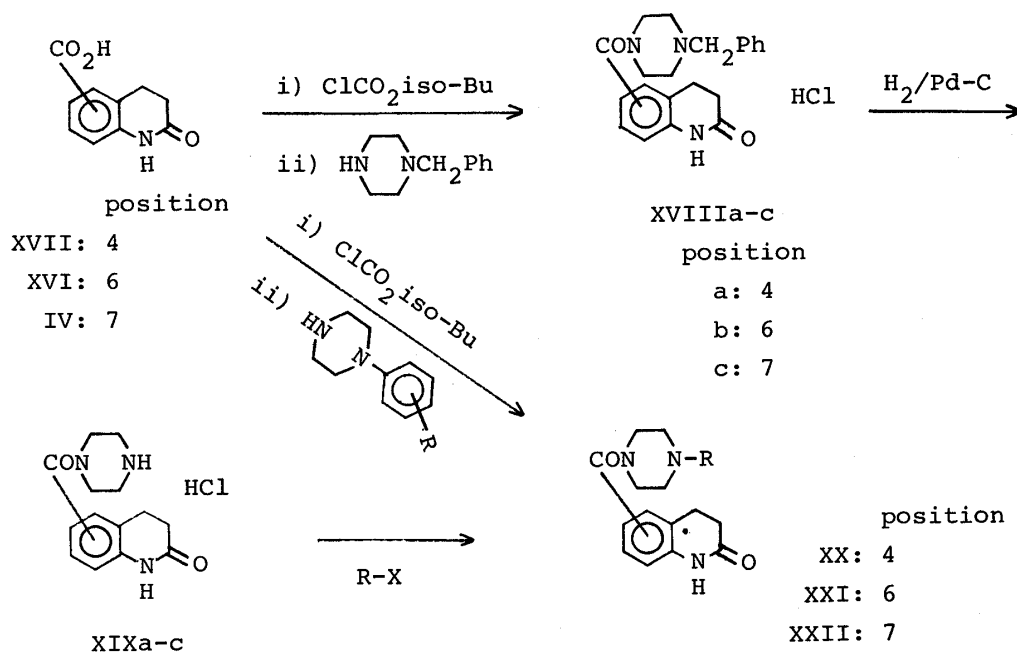
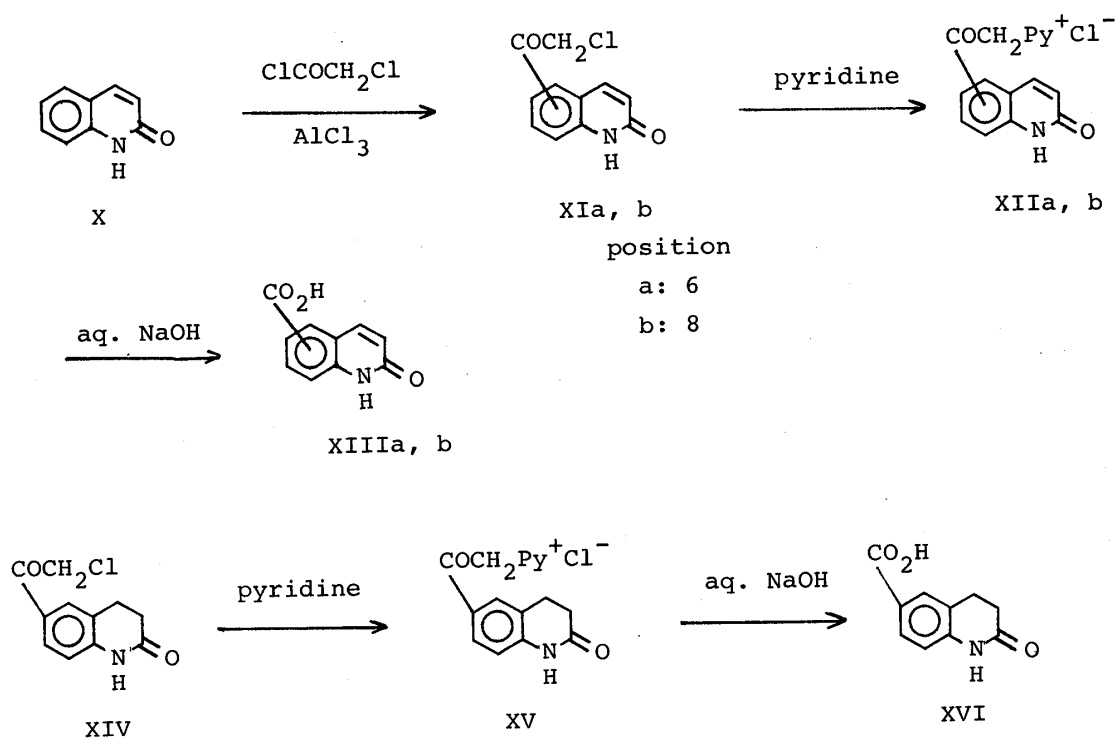
Chart 2

VI was achieved using sulfuric acid⁵⁾ at 50 °C to give VII in 51% yield. In this cyclization, a mixture of VII and 1,2-dihydro-2-oxo-7-quinolinecarboxylic acid (VIII) may be formed, but VIII could not be isolated. In the proton nuclear magnetic resonance (¹H-NMR) spectrum, the spin-spin coupling constants of aromatic protons showed that compound VII had three aromatic protons adjacent to each other. Moreover the ¹H-NMR and infrared (IR) spectra of the hydrogenated product (IX) were not identical with those of IV.

Finally, the 6-, and 8-carboxylic acid derivatives (XIIIa, b, XVI) were prepared by alkaline cleavage of β -ketoalkylpyridinium chloride⁶⁾ (Chart 3).

The Friedel-Crafts reaction of chloroacetyl chloride with 2(1*H*)-quinolinone (X) using anhydrous aluminium chloride in dichloromethane afforded chloroacetyl derivatives (XIa, b) in 50% and 20% yields, respectively. Compounds XIa and XIb were readily separated by column chromatography. Compounds XIa, b and 6-chloroacetyl-3,4-dihydro-2(1*H*)-quinolinone (XIV)⁷⁾ were converted to pyridinium salts (XIIa, b, XV) in good yield in the presence of excess pyridine, then cleaved by heating with aqueous sodium hydroxide to give the corresponding carboxylic acid derivatives XIIIa, b and XVI, and the structures of these compounds were confirmed by ¹H-NMR spectral analysis.

Synthesis of (4-substituted 1-piperazinylcarbonyl)-2(1*H*)-quinolinone derivatives was achieved from the corresponding carboxylic acid derivatives (Charts 4, 5). Preparations of



1,2,3,4-tetrahydro-2-oxo-4-quinolinecarboxylic acid (XVII)⁸⁾ and 1,2-dihydro-2-oxo-3-, and -4-quinolinecarboxylic acids (XXIII, XXIV)^{9,10)} have already been reported. Benzylpiperazine derivatives (XVIIIa—c, XXVa—e) were prepared from benzylpiperazine and the corresponding carboxylic acids by the ordinary mixed anhydride method using iso-butyl chloroformate (Table I). Hydrogenolysis of XVIIIa—c and XXVa—e over 10% palladium on charcoal gave piperazine derivatives (XIXa—c, XXVIa—e) (Table II).

Various (4-substituted 1-piperazinylcarbonyl)-2(1H)-quinolinone derivatives (XX—XXII and XXVII—XXXI) were obtained in the usual manner using appropriate alkyl halides

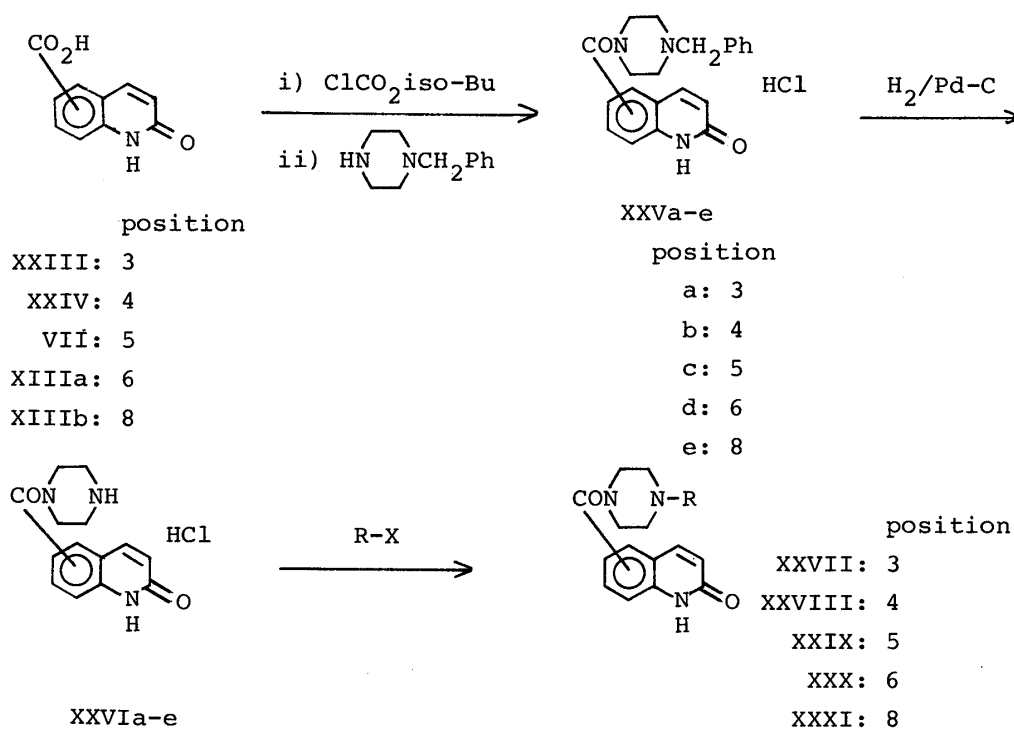
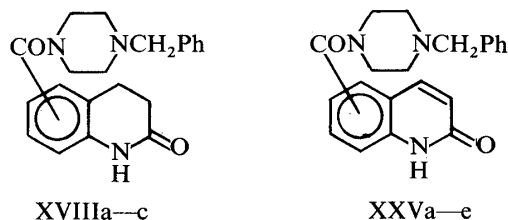
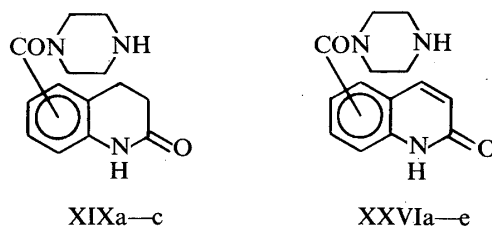


Chart 5

TABLE I. (4-Benzyl-1-piperazinylcarbonyl)-2(1*H*)-quinolinone Derivatives

Compd. No.	Position	Yield (%)	Form	mp (°C)	Recrystn. solvent	Formula	Analysis (%)		
							Calcd (Found)		
							C	H	N
XVIIIa	4	35	HCl	265.5—267 (dec.)	EtOH—H ₂ O	C ₂₁ H ₂₃ N ₃ O ₂ · HCl · 3/2 H ₂ O	61.08 (60.95)	6.59 (6.38)	10.18 (10.11)
XVIIIb	6	50	HCl	272—274	EtOH—H ₂ O	C ₂₁ H ₂₃ N ₃ O ₂ · HCl	65.36 (65.05)	6.27 (6.27)	10.89 (10.72)
XVIIIc	7	51	HCl	260—262	EtOH—H ₂ O	C ₂₁ H ₂₃ N ₃ O ₂ · HCl	65.36 (64.91)	6.27 (6.34)	10.89 (10.82)
XXVa	3	91	HCl	291—294 (dec.)	MeOH—H ₂ O	C ₂₁ H ₂₁ N ₃ O ₂ · HCl	65.70 (65.89)	5.78 (5.84)	10.95 (11.09)
XXVb	4	28	HCl	265—267 (dec.)	EtOH—H ₂ O	C ₂₁ H ₂₁ N ₃ O ₂ · HCl · 1/2 H ₂ O	64.20 (64.19)	5.90 (5.78)	10.70 (10.79)
XXVc	5	34	HCl	204—207	EtOH—H ₂ O	C ₂₁ H ₂₁ N ₃ O ₂ · HCl · 1/4 H ₂ O	64.95 (64.88)	5.84 (5.64)	10.82 (10.95)
XXVd	6	41	HCl	> 300	EtOH—H ₂ O	C ₂₁ H ₂₁ N ₃ O ₂ · HCl · H ₂ O	62.76 (62.57)	6.02 (6.29)	10.46 (10.55)
XXVe	8	49	HCl	177—180	EtOH	C ₂₁ H ₂₁ N ₃ O ₂ · HCl · 3/2 H ₂ O	61.39 (61.39)	6.13 (5.90)	10.23 (10.11)

TABLE II. (1-Piperazinylcarbonyl)-2(1*H*)-quinolinone Derivatives

Compd. No.	Position	Yield (%)	Form	mp (°C)	Recrystn. solvent	Formula	Analysis (%)		
							Calcd	Found	
							C	H	N
XIXa	4	54	HCl	179—183 (dec.)	EtOH—H ₂ O	C ₁₄ H ₁₇ N ₃ O ₂ · HCl · H ₂ O	53.59 (53.70)	6.42 (6.41)	13.39 (13.64)
XIXb	6	91	HCl	> 300	EtOH—H ₂ O	C ₁₄ H ₁₇ N ₃ O ₂ · HCl	56.85 (56.82)	6.13 (6.05)	14.21 (14.12)
XIXc	7	55	HCl	261.5—263	EtOH—H ₂ O	C ₁₄ H ₁₇ N ₃ O ₂ · HCl	56.85 (56.69)	6.13 (5.85)	14.21 (14.05)
XXVIa	3	93	HCl	> 300	EtOH—H ₂ O	C ₁₄ H ₁₅ N ₃ O ₂ · HCl · 1/2 H ₂ O	55.54 (55.58)	5.66 (5.68)	13.88 (13.95)
XXVIb	4	95	HCl	> 300	EtOH—H ₂ O	C ₁₄ H ₁₅ N ₃ O ₂ · HCl · H ₂ O	53.93 (53.76)	5.82 (5.70)	13.48 (13.61)
XXVIc	5	96	HCl	> 300	MeOH—H ₂ O	C ₁₄ H ₁₅ N ₃ O ₂ · HCl · H ₂ O	53.93 (53.70)	5.82 (5.94)	13.48 (13.26)
XXVI d	6	89	HCl	> 300	EtOH—H ₂ O	C ₁₄ H ₁₅ N ₃ O ₂ · HCl	57.24 (57.03)	5.49 (5.47)	14.31 (14.33)
XXVIe	8	69	HCl	> 300	EtOH—H ₂ O	C ₁₄ H ₁₅ N ₃ O ₂ · HCl · 1/4 H ₂ O	56.38 (56.47)	5.58 (5.42)	14.09 (14.36)

or acyl halides (Tables III, IV). Phenylpiperazine derivatives (XXIa—c) were obtained from 1,2,3,4-tetrahydro-2-oxo-6-quinolinecarboxylic acid by the mixed anhydride method.

Biological Activity

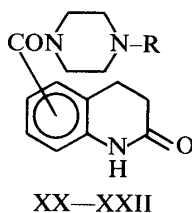
Some of the 2(1*H*)-quinolinone derivatives are listed in Table V. The inotropic and chronotropic effects of these compounds were compared with those of amrinone.¹¹⁾ As for the relationship between activity and position of substitution, the 6-substituted isomers exhibited potent positive inotropic activity, while other positional isomers were practically inactive. Thus, our studies were focused on the synthesis of 6-(4-substituted 1-piperazinylcarbonyl)-2(1*H*)-quinolinone derivatives.

The *N*-substituents of the piperazine ring substantially affected the activity. The alkyl, benzoyl alkyl, phenoxy alkyl and phenyl alkyl derivatives showed high potency, whereas the benzoyl derivatives showed little activity. Among these compounds, XXIa, b, j, l, m, t, and XXVd showed greater positive inotropic activities than amrinone. Among them, compounds XXIj and XXII showed little chronotropic activity. More detailed studies on compounds XXIj and XXII will be reported elsewhere.

Experimental

All melting points are uncorrected. IR spectra were recorded on a JASCO IRA-2 spectrometer. NMR spectra were recorded on a Varian EM-390 or JEOL JNM-FX200 NMR spectrometer using tetramethylsilane or 3-(trimethylsilyl)propionic acid-*d*₅ as an internal standard.

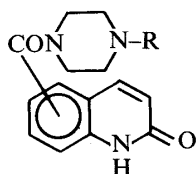
Methyl 3-(4-Chloroacetylphenyl)propionate (II)—AlCl₃ (122 g) was added portionwise to a suspension of

TABLE III. (4-Substituted 1-piperazinyldicarbonyl)-3,4-dihydro-2(1*H*)-quinolinone Derivatives

Compd. No.	Position	R	Yield (%)	Form	mp (°C)	Recrystn. solvent	Formula	Analysis (%)		
								Calcd	Found	
								C	H	N
XXa	4	(CH ₂) ₂ COPh	47	—	259—260 (dec.)	EtOH	C ₂₃ H ₂₅ N ₃ O ₃	70.57 (70.68)	6.44 (6.50)	10.74 (10.63)
XXIa	6		17	—	200—201	iso-PrOH	C ₂₀ H ₂₁ N ₃ O ₂	71.62 (71.63)	6.31 (6.22)	12.53 (12.58)
XXIb	6		47	—	226—227.5	EtOH—CHCl ₃	C ₂₁ H ₂₃ N ₃ O ₃	69.02 (69.06)	6.34 (6.26)	11.50 (11.38)
XXIc	6		19	—	210—211	MeOH	C ₂₁ H ₂₂ ClN ₃ O ₂	65.70 (65.76)	5.78 (5.77)	10.95 (10.92)
XXId	6		33	HCl	240—242 (dec.)	MeOH—Et ₂ O	C ₂₃ H ₂₇ N ₃ O ₄ · HCl · 1/2 H ₂ O	60.72 (60.68)	6.43 (6.41)	9.24 (9.18)
XXIe	6		37	HCl	262—264 (dec.)	EtOH—H ₂ O	C ₂₂ H ₂₅ N ₃ O ₃ · HCl	63.53 (63.23)	6.30 (6.11)	10.10 (9.91)
XXIf	6		51	HCl	> 300	EtOH—H ₂ O	C ₂₁ H ₂₂ ClN ₃ O ₂ · HCl	60.00 (60.29)	5.52 (5.51)	10.00 (10.12)
XXIg	6	(CH ₂) ₂ Ph	49	HCl	269—272 (dec.)	MeOH	C ₂₂ H ₂₅ N ₃ O ₂ · HCl · 1/2 H ₂ O	64.62 (64.41)	6.66 (6.36)	10.28 (10.29)
XXIh	6		84	—	238—239.5	EtOH—CHCl ₃	C ₂₃ H ₂₅ N ₃ O ₅	65.23 (65.25)	5.95 (6.10)	9.92 (9.85)
XXIi	6	CH ₂ COPh	30	HCl	212—215	EtOH—H ₂ O	C ₂₂ H ₂₃ N ₃ O ₃ · HCl · 1/2 H ₂ O	62.48 (62.51)	5.95 (5.72)	9.94 (9.97)
XXIj	6	(CH ₂) ₂ COPh	30	HCl	205—207 (dec.)	EtOH—H ₂ O	C ₂₃ H ₂₅ N ₃ O ₃ · HCl	64.55 (64.26)	6.12 (6.10)	9.82 (10.08)
XXIk	6	(CH ₂) ₂ CO—	17	HCl	204—205 (dec.)	EtOH—H ₂ O	C ₂₄ H ₂₇ N ₃ O ₄ · HCl · H ₂ O	60.56 (60.77)	6.35 (6.34)	8.83 (8.75)
XXIl	6	(CH ₂) ₃ COPh	7.2	HCl	241—242.5	EtOH—H ₂ O	C ₂₄ H ₂₇ N ₃ O ₃ · HCl · 1/4 H ₂ O	64.56 (64.35)	6.43 (6.36)	9.41 (9.39)
XXIm	6	(CH ₂) ₅ COPh	27	HCl	239—242	EtOH—H ₂ O	C ₂₆ H ₃₁ N ₃ O ₃ · HCl · H ₂ O	63.99 (64.18)	7.02 (6.81)	8.61 (8.64)
XXIn	6	COCH ₂ —	14	—	158—160	EtOH—Et ₂ O	C ₂₃ H ₂₅ N ₃ O ₄	67.79 (67.72)	6.18 (6.17)	10.31 (10.27)
XXIo	6	CO ₂ Et	48	—	180—182	MeOH	C ₁₇ H ₂₁ N ₃ O ₄	61.62 (61.38)	6.39 (6.31)	12.68 (12.61)
XXIip	6	(CH ₂) ₂ Oph	44	HCl	271—274 (dec.)	EtOH—H ₂ O	C ₂₂ H ₂₅ N ₃ O ₃ · HCl	63.53 (63.23)	6.30 (6.18)	10.10 (9.97)
XXIq	6	(CH ₂) ₂ O—	20	HCl	270—272 (dec.)	EtOH—H ₂ O	C ₂₃ H ₂₇ N ₃ O ₄ · HCl	61.94 (61.69)	6.33 (6.24)	9.42 (9.48)

TABLE III. (continued)

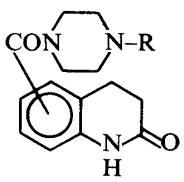
Compd. No.	Position	R	Yield (%)	Form	mp (°C)	Recrystn. solvent	Formula	Analysis (%)		
								Calcd	(Found)	
								C	H	N
XXIr	6	(CH ₂) ₃ OPh	26	HCl	151—153 (dec.)	EtOH—H ₂ O	C ₂₃ H ₂₇ N ₃ O ₃ · HCl	64.25 (64.05)	6.56 (6.58)	9.77 (9.72)
XXIs	6	<i>n</i> -Pr	26	HCl	259—262	EtOH	C ₁₇ H ₂₃ N ₃ O ₂ · HCl · 1/2 H ₂ O	58.86 (58.85)	7.26 (7.18)	12.12 (12.31)
XXIt	6	iso-C ₄ H ₉	47	HCl	292—293.5 (dec.)	MeOH—Et ₂ O	C ₁₈ H ₂₅ N ₃ O ₂ · HCl	61.44 (61.28)	7.45 (7.15)	11.94 (11.81)
XXIIa	7	(CH ₂) ₂ COPh	56	HCl	205—208 (dec.)	MeOH—H ₂ O	C ₂₂ H ₂₅ N ₃ O ₃ · HCl · 1/2 H ₂ O	62.18 (62.47)	6.41 (6.52)	9.89 (9.62)
XXIIb	7	(CH ₂) ₂ OPh	55	HCl	177—180	EtOH—H ₂ O	C ₂₂ H ₂₅ N ₃ O ₃ · HCl	63.53 (63.42)	6.30 (6.43)	10.10 (10.11)

TABLE IV. (4-Substituted 1-piperazinylcarbonyl)-2(1*H*)-quinolinone Derivatives

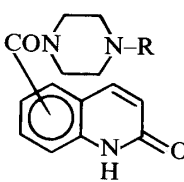
XXVII—XXXI

Compd. No.	Position	R	Yield (%)	Form	mp (°C)	Recrystn. solvent	Formula	Analysis (%)		
								Calcd	(Found)	
								C	H	N
XXVIIa	3	(CH ₂) ₂ OPh	13	HCl	280—282.5 (dec.)	MeOH	C ₂₂ H ₂₃ N ₃ O ₃ · HCl	63.84 (63.66)	5.85 (5.85)	10.15 (10.10)
XXVIIb	3	iso-C ₄ H ₉	1.7	HCl	281—282 (dec.)	EtOH—H ₂ O	C ₁₈ H ₂₃ N ₃ O ₂ · HCl · 1/2 H ₂ O	60.24 (60.52)	7.02 (6.75)	11.71 (11.47)
XXVIIIa	4	(CH ₂) ₂ COPh	22	HCl	207—209 (dec.)	MeOH—H ₂ O	C ₂₃ H ₂₃ N ₃ O ₃ · HCl · 1/4 H ₂ O	64.18 (64.07)	5.74 (5.54)	9.76 (9.67)
XXVIIIb	4	iso-C ₄ H ₉	14	HCl	278—281.5 (dec.)	MeOH	C ₁₈ H ₂₃ N ₃ O ₂ · HCl · 3/2 H ₂ O	57.36 (57.58)	7.22 (6.95)	11.15 (11.27)
XXVIIIc	4	(CH ₂) ₂ OPh	31	HCl	255.5—257 (dec.)	EtOH—H ₂ O	C ₂₂ H ₂₃ N ₃ O ₃ · HCl · H ₂ O	61.18 (61.00)	6.07 (5.88)	9.73 (9.82)
XXIXa	5	iso-C ₄ H ₉	42	HCl	251—254 (dec.)	MeOH	C ₁₈ H ₂₃ N ₃ O ₂ · HCl · 1/2 H ₂ O	60.25 (60.29)	7.02 (6.93)	11.71 (11.70)
XXIXb	5	(CH ₂) ₂ OPh	50	HCl	227—229	iso-PrOH	C ₂₂ H ₂₃ N ₃ O ₃ · HCl	63.84 (63.93)	5.85 (5.97)	10.15 (10.17)
XXIXc	5	(CH ₂) ₂ COPh	12	HCl	181.5—184	EtOH	C ₂₃ H ₂₃ N ₃ O ₃ · HCl · 3/4 H ₂ O	62.86 (62.86)	5.85 (5.66)	9.56 (9.53)
XXXa	6	(CH ₂) ₂ OPh	60	HCl	286—289 (dec.)	EtOH—H ₂ O	C ₂₂ H ₂₃ N ₃ O ₃ · HCl	63.83 (63.84)	5.85 (5.80)	10.15 (10.21)
XXXb	6	iso-C ₄ H ₉	16	HCl	>300	MeOH	C ₁₈ H ₂₃ N ₃ O ₂ · HCl · 1/2 H ₂ O	60.24 (60.44)	7.02 (6.87)	11.71 (11.89)
XXXc	6	(CH ₂) ₃ Ph	21	HCl	290—293 (dec.)	EtOH—H ₂ O	C ₂₃ H ₂₅ N ₃ O ₂ · HCl	67.06 (66.84)	6.36 (6.29)	10.20 (10.24)
XXXia	8	(CH ₂) ₂ COPh	38	HCl	182—184	MeOH	C ₂₃ H ₂₃ N ₃ O ₃ · HCl	64.86 (64.80)	5.68 (5.67)	9.87 (9.85)
XXXIb	8	iso-C ₄ H ₉	7	HCl	284—288 (dec.)	MeOH	C ₁₈ H ₂₃ N ₃ O ₂ · HCl · 1/4 H ₂ O	61.01 (61.13)	6.97 (6.79)	11.86 (12.16)

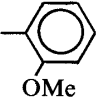
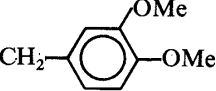
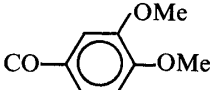
TABLE V. Biological Activity of 2(1*H*)-quinolinone Derivatives on the Canine Heart (*n* = 1)



XVIII, XX, XXI, XXII



XXV, XXVII, XXIX, XXXI

Compd. No.	Position	R	Inotropic effect	Chronotropic effect
XVIIIb	6	CH ₂ Ph	1.0	LE
XXa	4	(CH ₂) ₂ COPh	LE	LE
XXIa	6	Ph	5.4	3.4
XXIb	6		1.8	0.8
XXId	6		0.3	LE
XXIg	6	(CH ₂) ₂ Ph	1.0	3.3
XXIh	6		0.2	0.2
XXIj	6	(CH ₂) ₂ COPh	3.9	LE
XXII	6	(CH ₂) ₃ COPh	1.7	LE
XXIm	6	(CH ₂) ₅ COPh	1.1	LE
XXIp	6	(CH ₂) ₂ OPh	0.9	LE
XXIt	6	iso-C ₄ H ₉	1.8	0.1
XXIIa	7	(CH ₂) ₂ COPh	LE	LE
XXVd	6	CH ₂ Ph	1.3	2.8
XXVIIb	3	iso-C ₄ H ₉	LE	LE
XXIXc	5	(CH ₂) ₂ COPh	LE	LE
XXXIa	8	(CH ₂) ₂ COPh	LE	LE

The potency of inotropic and chronotropic effects of the test compounds was evaluated at doses (ED 50%) producing the half-maximal response to amrinone as follows. Activity ratio of test compound = ED 50% of amrinone/dose of test compound producing the same response as ED 50% of amrinone. The larger the activity ratio, the more potent is the test drug. The highest dose (1 μ mol) of amrinone used in these experiments increased developed tension by about 50% of the basal tension, and increased sinus rate by about 15 beats/min. LE means lower than 0.1 activity ratio.

methyl hydrocinnamate (I) (50 g) and chloroacetyl chloride (51.6 g) in CH₂Cl₂ (250 ml) at 0–10 °C. After the addition, the mixture was stirred at room temperature for 2 h, and allowed to stand overnight. The reaction mixture was poured into ice-water and extracted with CHCl₃. The extract was washed with H₂O, dried (Na₂SO₄) and concentrated *in vacuo*. The residue was recrystallized from EtOH to give II (53.4 g, 71%) as colorless needles, mp 90–92 °C. IR $\nu_{\text{max}}^{\text{KBr}}$ cm⁻¹: 1730, 1695, 1605. NMR (CDCl₃) δ : 2.51–3.18 (4H, m, CH₂CH₂COO), 3.67 (3H, s, COOCH₃), 4.68 (2H, s, COCH₂Cl), 7.32 (2H, d, *J* = 12 Hz, aromatic H), 7.88 (2H, d, *J* = 12 Hz, aromatic H). Anal. Calcd for C₁₂H₁₃ClO₃: C, 59.88; H, 5.44. Found: C, 59.64; H, 5.41.

4-(2-Methoxycarbonylethyl)-3-nitrobenzoic Acid (III)—Fuming HNO₃ (20.9 g, *d* = 1.52) was added dropwise to a solution of II (36.3 g) in conc. H₂SO₄ (300 ml) with stirring and ice-cooling. The mixture was stirred at room temperature for 3 h, then poured into ice-water and extracted with CHCl₃. The extract was washed with water, dried (Na₂SO₄) and concentrated *in vacuo*. The residue was recrystallized from MeOH to give III (26.7 g, 70%) as pale yellow prisms, mp 120–122 °C. IR $\nu_{\text{max}}^{\text{KBr}}$ cm⁻¹: 3100, 1735, 1685, 1615, 1530. NMR (DMSO-*d*₆) δ : 2.74 (2H, t, *J* = 7 Hz, CH₂), 3.17 (2H, t, *J* = 7 Hz, CH₂), 3.60 (3H, s, OCH₃), 7.70 (1H, d, *J* = 8 Hz, aromatic H), 8.16 (1H, dd, *J*₁ = 8 Hz, *J*₂ = 2 Hz, aromatic H), 8.40 (1H, d, *J* = 2 Hz, aromatic H), 13.27 (1H, br, COOH). Anal. Calcd for C₁₁H₁₁NO₆:

C, 52.17; H, 4.38; N, 5.53. Found: C, 52.16; H, 4.24; N, 5.72.

1,2,3,4-Tetrahydro-2-oxo-7-quinolinecarboxylic Acid (IV)—A mixture of III (5.0 g), 5% palladium on charcoal (0.5 g), NaOH (0.9 g) and MeOH (100 ml) was stirred at room temperature under atmospheric pressure of hydrogen until the absorption of hydrogen ceased. The catalyst was filtered off and conc. HCl was added to the filtrate. The resulting precipitate was collected by filtration and washed with acetone. Recrystallization from MeOH gave IV (3.6 g, 95%) as colorless needles, mp $> 300^{\circ}\text{C}$. IR $\nu_{\text{max}}^{\text{KBr}} \text{cm}^{-1}$: 3270, 1695, 1635, 1585, 1390. NMR (DMSO- d_6) δ : 2.42–2.54, 2.89–3.01 (each 2H, m, $-\text{CH}_2\text{CH}_2-$), 7.29 (1H, d, $J=8$ Hz, C_5 -aromatic H), 7.48 (1H, d, $J=1.5$ Hz, C_8 -aromatic H), 7.05 (1H, dd, $J_1=8$ Hz, $J_2=1.5$ Hz, C_6 -aromatic H), 10.24 (1H, s, CONH), 12.91 (1H, br, COOH). Anal. Calcd for $\text{C}_{10}\text{H}_9\text{NO}_3$: C, 62.82; H, 4.75; N, 7.33. Found: C, 62.94; H, 4.81; N, 7.14.

3-[N-(3-Ethoxy-1-oxo-2-propenyl)amino]benzoic Acid (VI)— β -Ethoxyacryloyl chloride (44.6 g) was added dropwise to a mixture of *m*-aminobenzoic acid (V) (100 g) in dry ether (1000 ml) with stirring at room temperature. The mixture was stirred for 5 h at 40°C , then allowed to cool. The precipitate was collected by filtration and washed with warm water. Recrystallization from methanol gave VI (60 g, 77%) as colorless needles, mp $200.5\text{--}202^{\circ}\text{C}$. IR $\nu_{\text{max}}^{\text{KBr}} \text{cm}^{-1}$: 3260, 1685, 1660, 1610, 1590. NMR (DMSO- d_6) δ : 1.27 (3H, t, $J=6.5$ Hz, OCH_2CH_3), 3.92 (2H, q, $J=6.5$ Hz, OCH_2), 5.53 (1H, d, $J=12$ Hz, NHCOCH=), 7.18–7.33 (4H, m, aromatic H), 7.46 (1H, d, $J=12$ Hz, NHCOCH=CH), 9.87 (1H, s, CONH), 12.54 (1H, br, COOH). Anal. Calcd for $\text{C}_{12}\text{H}_{13}\text{NO}_4$: C, 61.27; H, 5.57; N, 5.95. Found: C, 61.31; H, 5.43; N, 6.03.

1,2-Dihydro-2-oxo-5-quinolinecarboxylic Acid (VII)—A solution of VI (59 g) in conc. H_2SO_4 (600 ml) was stirred at $40\text{--}50^{\circ}\text{C}$ for 3 h, then poured into ice-water. The precipitate was collected by filtration and washed with MeOH. Recrystallization from dimethylformamide (DMF) gave VII as a white powder (39 g, 51%), mp $277.5\text{--}279^{\circ}\text{C}$. IR $\nu_{\text{max}}^{\text{KBr}} \text{cm}^{-1}$: 1710, 1675, 1640 (sh), 1600, 1504. NMR (DMSO- d_6) δ : 6.64 (1H, d, $J=10$ Hz, NHCOCH=), 7.54, 7.75 (each 1H, dd, $J_1=7$ Hz, $J_2=1$ Hz, C_6 -, C_8 -aromatic H), 7.06 (1H, dd, $J_1=J_2=7$ Hz, C_7 -aromatic H), 8.77 (1H, d, $J=10$ Hz, NHCOCH=CH), 11.97 (1H, br, CONH), 13.10 (1H, br, COOH). Anal. Calcd for $\text{C}_{10}\text{H}_7\text{NO}_3$: C, 63.49; H, 3.73; N, 7.41. Found: C, 63.45; H, 4.00; N, 7.65.

1,2,3,4-Tetrahydro-2-oxo-5-quinolinecarboxylic Acid (IX)—A mixture of VII (2.0 g), 10% palladium on charcoal (0.5 g) and NaOH (0.6 g) in H_2O (30 ml) was stirred at room temperature under 3–4 atm of hydrogen until the absorption of hydrogen ceased. The catalyst was filtered off, and conc. HCl was added to the filtrate. The resulting precipitate was collected by filtration and washed with acetone. Recrystallization from MeOH gave IX (1.4 g, 70%) as colorless needles, mp $309\text{--}311^{\circ}\text{C}$. IR $\nu_{\text{max}}^{\text{KBr}} \text{cm}^{-1}$: 3070, 2660, 1685, 1650 (sh), 1590. NMR (DMSO- d_6) δ : 2.27–2.62, 2.91–3.51 (each 2H, m, $\text{CH}_2\text{CH}_2\text{CONH}$), 7.05 (1H, d, $J=8$ Hz, C_8 -aromatic H), 7.24 (1H, dd, $J_1=J_2=8$ Hz, C_7 -aromatic H), 7.43 (1H, d, $J=8$ Hz, C_6 -aromatic H), 10.19 (1H, s, CONH), 12.95 (1H, br, COOH). Anal. Calcd for $\text{C}_{10}\text{H}_9\text{NO}_3$: C, 62.82; H, 4.75; N, 7.33. Found: C, 62.80; H, 4.77; N, 7.17.

6-Chloroacetyl-2(1H)-quinolinone (XIa) and 8-Chloroacetyl-2(1H)-quinolinone (XIb)—A mixture of AlCl_3 (83 g) and chloroacetyl chloride (33 ml) in CH_2Cl_2 (60 ml) was stirred at room temperature for 0.5 h. 2(1H)-Quinolinone (X) was added portionwise to the suspension over 0.5 h. After the addition, the mixture was heated under reflux for 6 h, then poured into ice-water. The precipitates were collected by filtration and washed with water to give a mixture of XIa and XIb. The mixture was washed with hot MeOH and recrystallized from DMF to give XIa (23 g, 50%) as pale yellow needles. Compound XIb was obtained from the methanolic filtrate. The filtrate was concentrated *in vacuo*, and the residue was chromatographed over silica gel then recrystallized from MeOH to give XIb (9 g, 20%) as pale yellow needles.

XIa: mp $274.5\text{--}277^{\circ}\text{C}$ (dec.). IR $\nu_{\text{max}}^{\text{KBr}} \text{cm}^{-1}$: 3270, 1690, 1655, 1615, 1170. NMR (DMSO- d_6) δ : 5.26 (2H, s, COCH_2Cl), 6.67 (1H, d, $J=10.5$ Hz, NHCOCH=), 7.51 (1H, d, $J=9$ Hz, C_8 -aromatic H), 8.12 (1H, d, $J=10.5$ Hz, NHCOCH=CH), 8.18 (1H, dd, $J_1=9$ Hz, $J_2=2$ Hz, C_7 -aromatic H), 8.49 (1H, d, $J=2$ Hz, C_5 -aromatic H), 12.09 (1H, br, CONH). Anal. Calcd for $\text{C}_{11}\text{H}_8\text{ClNO}_2$: C, 59.61; H, 3.64; N, 6.32. Found: C, 59.47; H, 3.63; N, 6.33.

XIb: mp $177.5\text{--}179^{\circ}\text{C}$. IR $\nu_{\text{max}}^{\text{KBr}} \text{cm}^{-1}$: 3290, 1645, 1600, 1570, 1405. NMR (DMSO- d_6) δ : 4.74 (2H, s, COCH_2Cl), 6.72 (1H, dd, $J_1=9.5$ Hz, $J_2=2$ Hz, NHCOCH=CH), 7.29 (1H, dd, $J_1=J_2=8$ Hz, C_6 -aromatic H), 7.75 (1H, dd, $J=9.5$ Hz, NHCOCH=CH), 7.82, 8.09 (each 1H, dd, $J_1=8$ Hz, $J_2=1.5$ Hz, C_5 -, C_8 -aromatic H), 12.10 (1H, br, CONH). Anal. Calcd for $\text{C}_{11}\text{H}_8\text{ClNO}_2$: C, 59.61; H, 3.64; N, 6.32. Found: C, 59.43; H, 3.60; N, 6.31.

Preparation of Pyridinium Salts (XIIa, b, XV). 1-[2-(1,2-Dihydro-2-oxo-6-quinolyl)-2-oxoethyl]pyridinium Chloride (XIIa)—A suspension of XIa (60 g) in pyridine (500 ml) was stirred at $80\text{--}90^{\circ}\text{C}$ for 2 h, then allowed to cool. The precipitate was collected by filtration and washed with EtOH. Recrystallization from H_2O –EtOH gave XIIa (70 g, 86%) as colorless needles, mp $> 300^{\circ}\text{C}$. IR $\nu_{\text{max}}^{\text{KBr}} \text{cm}^{-1}$: 3550, 3410, 1680, 1660, 1635. NMR (DMSO- d_6 + D_2O) δ : 4.40 (2H, s, COCH_2), 6.69 (1H, d, $J=9.5$ Hz, NHCOCH=), 7.49 (1H, d, $J=8$ Hz, C_8 -aromatic H), 8.01–9.01 (7H, m, aromatic H), 8.11 (1H, d, $J=9.5$ Hz, NHCOCH=CH). Anal. Calcd for: $\text{C}_{16}\text{H}_{13}\text{ClN}_2\text{O}_2 \cdot 1/2\text{H}_2\text{O}$: C, 62.04; H, 4.56; N, 9.05. Found: C, 61.83; H, 4.49; N, 9.02.

Compounds XIIb and XV were obtained in the same manner as described for XIIa.

Compound XIIb was recrystallized from MeOH to give colorless needles, mp $261.5\text{--}264^{\circ}\text{C}$ (dec.). IR $\nu_{\text{max}}^{\text{KBr}} \text{cm}^{-1}$: 3300, 3035, 1675, 1655, 1630. NMR (DMSO- d_6 + D_2O) δ : 4.30 (2H, s, COCH_2), 6.53 (1H, d, $J=11$ Hz, NHCOCH=), 7.37–9.02 (8H, m, aromatic H), 8.05 (1H, d, $J=11$ Hz, NHCOCH=CH). Anal. Calcd for $\text{C}_{16}\text{H}_{13}\text{ClN}_2\text{O}_2 \cdot 1/2\text{H}_2\text{O}$: C, 62.04; H, 4.56; N, 9.04. Found: C, 62.28; H, 4.32; N, 9.29.

Compound XV was recrystallized from MeOH-H₂O to give colorless needles mp 294–295 °C (dec.). IR $\nu_{\text{max}}^{\text{KBr}}$ cm⁻¹: 3550, 3400, 1670 (sh), 1635. NMR (DMSO-*d*₆+D₂O) δ : 2.39–3.25 (4H, m, CH₂CH₂), 4.36 (2H, s, COCH₂N), 7.07 (1H, d, *J*=9 Hz, C₈-aromatic H), 7.77–9.02 (7H, m, aromatic H). Anal. Calcd for C₁₆H₁₅ClN₂O₂: C, 63.48; H, 4.99; N, 9.25. Found: C, 63.59; H, 5.06; N, 9.26.

Preparation of Carboxylic Acids (XIIIa, b, XVI). 1,2-Dihydro-2-oxo-6-quinolinecarboxylic Acid (XIIIa)—A mixture of XIIa (69.7 g) and NaOH (65 g) in H₂O (600 ml) was stirred at 60–70 °C for 3 h, then allowed to cool. The mixture was acidified with conc. HCl to pH 2, then the resulting precipitates were collected by filtration and washed with MeOH. Recrystallization from DMF gave XIIIa (41.4 g, 94%) as light brown needles, mp >300 °C. IR $\nu_{\text{max}}^{\text{KBr}}$ cm⁻¹: 3030, 1720, 1645, 1555. NMR (DMSO-*d*₆) δ : 6.58 (1H, d, *J*=9 Hz, NHCOCH=), 7.37 (1H, d, *J*=8 Hz, C₈-aromatic H), 8.04 (1H, dd, *J*₁=8 Hz, *J*₂=2 Hz, C₇-aromatic H), 8.06 (1H, d, *J*=9 Hz, COCH=CH), 8.32 (1H, d, *J*=2 Hz, C₅-aromatic H), 12.07 (1H, br s, NHCO), 14.10 (1H, br, COOH). Anal. Calcd for C₁₀H₇NO₃: C, 63.49; H, 3.73; N, 7.41. Found: C, 63.43; H, 3.97; N, 7.61.

Compounds XIIIb and XVI were obtained in the same manner as described for XIIIa.

Compound XIIIb was recrystallized from MeOH-CHCl₃ to give colorless needles, mp >300 °C. IR $\nu_{\text{max}}^{\text{KBr}}$ cm⁻¹: 3225, 1680, 1640, 1630 (sh), 1560. NMR (DMSO-*d*₆) δ : 6.64 (1H, dd, *J*₁=10 Hz, *J*₂=1.5 Hz, NHCOCH=), 7.33 (1H, dd, *J*₁=*J*₂=8 Hz, C₆-aromatic H), 8.01, 8.22 (each 1H, dd, *J*₁=8 Hz, *J*₂=1.5 Hz, C₅-, C₇-aromatic H), 8.06 (1H, d, *J*=10 Hz, COCH=CH), 11.83 (1H, br s, CONH), 12.98 (1H, br, COOH). Anal. Calcd for C₁₀H₇NO₃: C, 63.49; H, 3.73; N, 7.41. Found: C, 63.49; H, 3.82; N, 7.28.

Compound XVI was recrystallized from DMF to give a pale yellow powder, mp >300 °C. IR $\nu_{\text{max}}^{\text{KBr}}$ cm⁻¹: 3200, 3075, 2560, 1680, 1650 (sh). NMR (DMSO-*d*₆) δ : 2.44–2.57, 2.72–3.02 (each 2H, m, CH₂CH₂), 6.93 (1H, d, *J*=9 Hz, C₈-aromatic H), 7.75 (1H, dd, *J*₁=9 Hz, *J*₂=1.5 Hz, C₇-aromatic H), 7.78 (1H, s, C₅-aromatic H), 10.40 (1H, s, CONH), 12.29 (1H, br, COOH). Anal. Calcd for C₁₀H₉NO₃: C, 62.82; H, 4.75; N, 7.33. Found: C, 62.64; H, 4.85; N, 7.48.

Preparation of (4-Benzyl-1-piperazinylcarbonyl)-2(1H)-quinolinone Derivatives (XVIIIa–c, XXVa–e). 6-(4-Benzyl-1-piperazinylcarbonyl)-3,4-dihydro-2(1H)-quinolinone (XVIIIb)—A solution of isobutyl chloroformate (31 g) in DMF (20 ml) was added dropwise to a stirred suspension of XVI (29 g) and Et₃N (25 ml) in DMF (180 ml) with ice-cooling, and the mixture was stirred at room temperature for 1 h. Then 1-benzylpiperazine (31 g) was added dropwise at room temperature. After the addition, the reaction mixture was stirred at room temperature for 3 h, then poured into 0.5 N NaOH. The whole was extracted with CHCl₃, and the extract was washed with water, dried (Na₂SO₄) and concentrated *in vacuo*. The residue was treated with MeOH containing HCl, and concentrated *in vacuo*. The residue was recrystallized from EtOH-H₂O to give XVIIIb (31.3 g, 50%) as colorless needles, mp 272–274 °C (dec.). IR $\nu_{\text{max}}^{\text{KBr}}$ cm⁻¹: 3070, 2560, 1690, 1665, 1650. NMR (DMSO-*d*₆) δ : 2.27–4.52 (14H, m, COCH₂CH₂, -N(CH₂CH₂)₂N-, N-CH₂-C₆H₅), 6.73–7.77 (8H, m, aromatic H), 10.23 (1H, s, CONH). The elemental analysis data are shown in Table I.

Compounds XVIIIa, c and XXVa–e were obtained in the same manner as described for XVIIIb. The yields, melting points and elemental analysis data are shown in Table I.

Preparation of Piperazinylcarbonyl-2(1H)-quinolinone Derivatives (XIXa–c, XXVIa–e). 3,4-Dihydro-6-(1-piperazinylcarbonyl)-2(1H)-quinolinone (XIXb)—A mixture of XVIIIb (20 g) and 10% palladium on charcoal (2 g) in EtOH (130 ml) and H₂O (70 ml) was stirred at 45–50 °C under atmospheric pressure of hydrogen until the absorption of hydrogen ceased. The catalyst was filtered off and the filtrate was concentrated *in vacuo*. The residue was recrystallized from EtOH-H₂O to give XIXb (14 g, 91%) as colorless scales, mp >300 °C. IR $\nu_{\text{max}}^{\text{KBr}}$ cm⁻¹: 3170, 3060, 2470, 1680, 1660. NMR (DMSO-*d*₆) δ : 2.22–3.93 (12H, COCH₂CH₂, -N(CH₂CH₂)₂N-), 7.41 (3H, m, aromatic H), 10.20 (1H, br, NH), 10.30 (1H, s, CONH). The elemental analysis data are shown in Table II.

Compounds XIXa, c and XXVIa–e were obtained in the same manner as described for XIXb. The yields, melting points and elemental analysis data are shown in Table II.

Preparation of XXIa–c. 6-[4-(3-Chloro-2-methylphenyl)-1-piperazinylcarbonyl]-3,4-dihydro-2(1H)-quinolinone (XXIc)—A solution of isobutyl chloroformate (0.84 g) in DMF (3 ml) was added dropwise to a stirred suspension of XVI (1.2 g) and Et₃N (0.97 ml) in DMF (15 ml) with ice-cooling, and the mixture was stirred at room temperature for 1 h. To this suspension was added dropwise a solution of 1-(3-chloro-2-methylphenyl)piperazine (1.6 g) in DMF (3 ml), and the mixture was stirred at room temperature for 5 h. The mixture was poured into NaCl solution and extracted with CHCl₃. The extract was washed with water, dried (Na₂SO₄) and concentrated *in vacuo*. The residue was recrystallized from MeOH to afford XXIc (0.46 g, 19%) as colorless needles, mp 210–211 °C. IR $\nu_{\text{max}}^{\text{KBr}}$ cm⁻¹: 1695, 1615, 1590, 1460, 1000. NMR (DMSO-*d*₆) δ : 2.15–3.09, 3.43–3.82 (12H, m, COCH₂CH₂, -N(CH₂CH₂)₂N-), 2.32 (3H, s, CH₃), 6.73–7.36 (6H, m, aromatic H), 10.18 (1H, br s, CONH). The elemental analysis data are shown in Table III.

Compounds XXIa, b were obtained in the same manner as described for XXIc. The yields, melting points and elemental analysis data are shown in Table III.

Preparation of XXId–g, i, s, t, XXVIIb, XXVIIIb, XXIXa, XXXb, c and XXXIb. 6-[4-(4-Chlorobenzyl)-1-piperazinylcarbonyl]-3,4-dihydro-2(1H)-quinolinone (XXIf)—A suspension of XIXb (3.0 g), Et₃N (4.0 ml) and *p*-chlorobenzyl chloride (3.1 g) in MeCN (20 ml) was stirred at 45–50 °C for 2.5 h. The mixture was concentrated *in*

vacuo. The residue was poured into saturated NaHCO_3 solution and extracted with CHCl_3 . The CHCl_3 layer was washed with water, dried (Na_2SO_4) and concentrated *in vacuo*. The residue was dissolved in acetone-MeOH and acidified with conc. HCl to pH 1. The resulting precipitates were collected by filtration, then recrystallized from EtOH-H₂O to give XXIf (2.5 g, 51%) as colorless needles, mp $> 300^\circ\text{C}$. IR $\nu_{\text{max}}^{\text{KBr}} \text{cm}^{-1}$: 3070, 2400, 1690, 1660, 1655. NMR ($\text{DMSO}-d_6$) δ : 2.19–4.60 (14H, m, $-\text{N}(\text{CH}_2\text{CH}_2)_2\text{N}-$, $\text{N}-\text{CH}_2$, $\text{NHCOCH}_2\text{CH}_2$), 6.78–7.85 (7H, m, aromatic H), 10.25 (1H, s, CONH). The elemental analysis data are shown in Table III.

Compounds XXId, e, g, i, s, t, XXVIIb, XXVIIIb, XXIXa, XXXb, c and XXXIb were obtained in the same manner as described for XXIf. The yields, melting points and elemental analysis data are shown in Tables III and IV.

Preparation of XXIIh, n, o. 6-[4-(3,4-Dimethoxybenzoyl)-1-piperazinylcarbonyl]-3,4-dihydro-2(1H)-quinolinone (XXIIh)—A solution of 3,4-dimethoxybenzoyl chloride (3.5 g) in CH_2Cl_2 (20 ml) was added dropwise to a suspension of XIXb (3 g) and Et_3N (3.5 ml) in CH_2Cl_2 (20 ml) with stirring and ice-cooling. After the addition, the mixture was stirred for 1 h at room temperature. The mixture was poured into saturated NaHCO_3 solution and extracted with CHCl_3 . The CHCl_3 layer was washed with water, dried (Na_2SO_4) and concentrated *in vacuo*. The residue was recrystallized from EtOH- CHCl_3 to give XXIIh. (3.6 g, 84%) as colorless prisms, mp $238\text{--}239.5^\circ\text{C}$. IR $\nu_{\text{max}}^{\text{KBr}} \text{cm}^{-1}$: 3240, 1710, 1685 (sh), 1680, 1625. NMR (CDCl_3) δ : 2.51–3.19 (4H, m, $\text{NHCOCH}_2\text{CH}_2$), 3.63 (8H, s, $-\text{N}(\text{CH}_2\text{CH}_2)_2\text{N}-$, 3.87 (6H, s, $2 \times \text{OCH}_3$), 6.70–7.30 (6H, m, aromatic H), 9.03 (1H, s, CONH). The elemental analysis data are shown in Table III.

Compounds XXIn, o were obtained in the same manner as described for XXIIh and the yields, melting points and elemental analysis data are shown in Table III.

Preparation of XXa, XXIIj—m, p, q, r, XXIIa, b, XXVIIa, XXVIIIa, c, XXIXb, c, XXXa, and XXXIa. 3,4-Dihydro-6-[4-(3-oxo-3-phenylpropyl)-1-piperazinylcarbonyl]-2(1H)-quinolinone (XXIIj)—A mixture of β -chloropropiophenone (5.5 g) and NaI (6 g) in DMF (100 ml) was stirred at $50\text{--}55^\circ\text{C}$ for 1 h. K_2CO_3 (9.3 g) and XIXb (8.0 g) were added to this suspension, and the mixture was stirred for 4 h at $70\text{--}80^\circ\text{C}$, then poured into 0.5 N NaOH solution and extracted with CHCl_3 . The extract was washed with water, dried (Na_2SO_4) and concentrated *in vacuo*. The residue was chromatographed over silica gel (eluent CHCl_3 : MeOH = 30 : 1), then dissolved in MeOH containing HCl. This solution was concentrated, and the residue was recrystallized from EtOH-H₂O to give XXIIj (3.33 g, 29%) as colorless scales, mp $205\text{--}207^\circ\text{C}$ (dec.). IR $\nu_{\text{max}}^{\text{KBr}} \text{cm}^{-1}$: 2570, 1675, 1645, 1615, 1595. NMR ($\text{DMSO}-d_6$) δ : 2.18–4.52 (16H, m, $-\text{N}(\text{CH}_2\text{CH}_2)_2\text{N}-$, $\text{NHCOCH}_2\text{CH}_2$, $\text{N}-\text{CH}_2\text{CH}_2\text{CO}$), 6.78–8.20 (8H, m, aromatic H), 10.24 (1H, s, CONH). The elemental analysis data are shown in Table III.

Compounds XXa, XXIk—m, p, q, r, XXIIa, b, XXVIIa, XXVIIIa, c, XXIXb, c, XXXa and XXXIa were obtained in the same manner as described for XXIIj, and the yield, melting point and elemental analysis data are shown in Tables III and IV.

Method of Pharmacological Studies

Inotropic and chronotropic effects of test compounds were examined by the use of isolated, blood-perfused dog heart preparations. The hearts were excised from mongrel dogs of either sex weighing 8–14 kg. The isolated, blood-perfused papillary muscle and sino-atrial node were prepared according to the methods of Endoh and Hashimoto (1970)¹² and Kubota and Hashimoto (1973),¹³ respectively. The preparations were cross-circulated through the cannulated arteries with blood from a donor dog anesthetized with sodium pentobarbital and receiving heparin. The perfusion pressure was kept constant at 100 mmHg. The papillary muscle was stimulated at a frequency of 2 Hz and tension developed by the muscle was measured with a force displacement transducer (Shinkoh, UL-20-240). Sinus rate was measured by the use of a cardi tachometer (Data Graph, T-149) triggered by developed tension of the right atrium. Blood flow through the cannulated arteries was measured with an electromagnetic flow meter (Nihon Kohden, MF-27). Recording of these parameters was done on an ink-writing rectigraph (Sanei Instrument, 8S). The compounds were injected intraarterially with microsyringes.

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