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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 (XXIl) were found to have potent activity.

Keywords——congestive heart failure; positive inotropic agent; 1,2-dihydro-2-oxoquinolinecarboxylic 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-methoxycarbonylethyl)-2-nitrobenzoic acid (III) (Chart 1). Methyl 3-(4-chloroacetylphenyl)propionate[2] (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 chloride[4] gave VI in 77% yield. Cyclization of

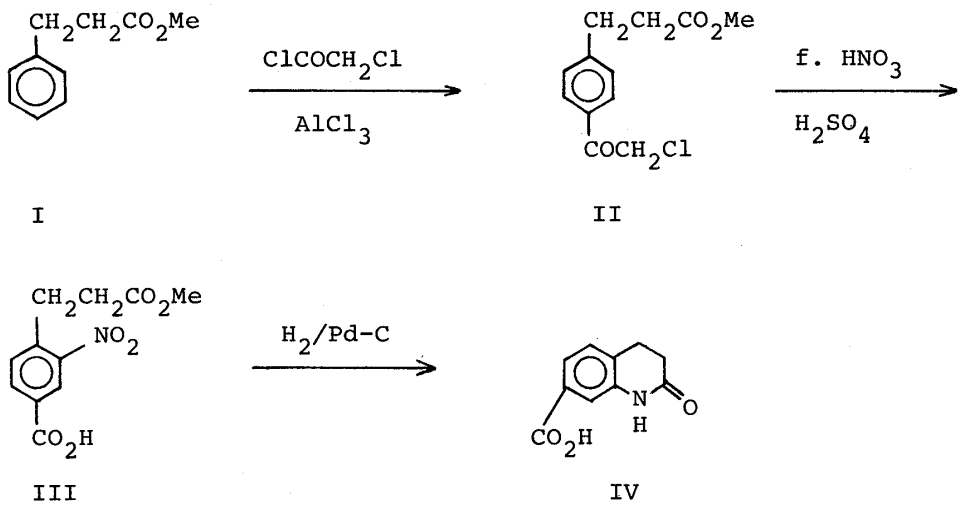


Chart 1

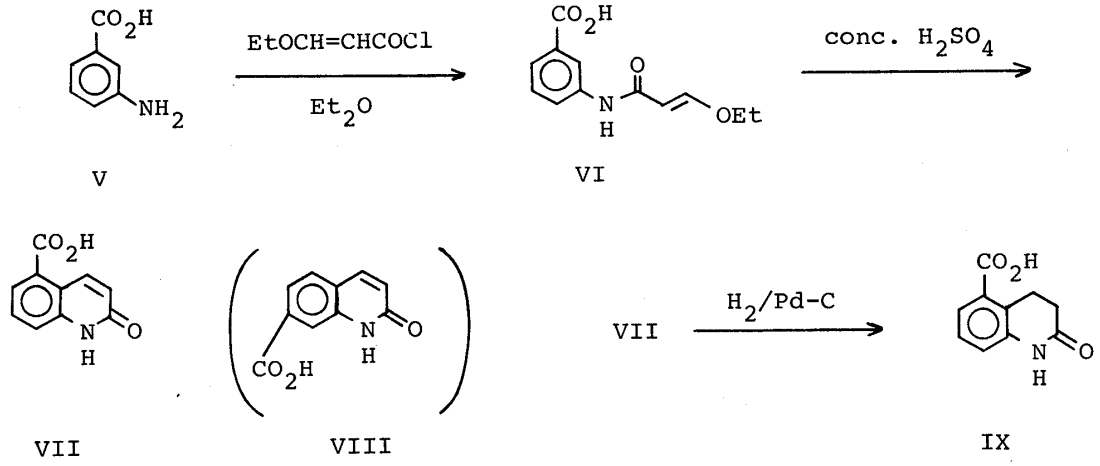


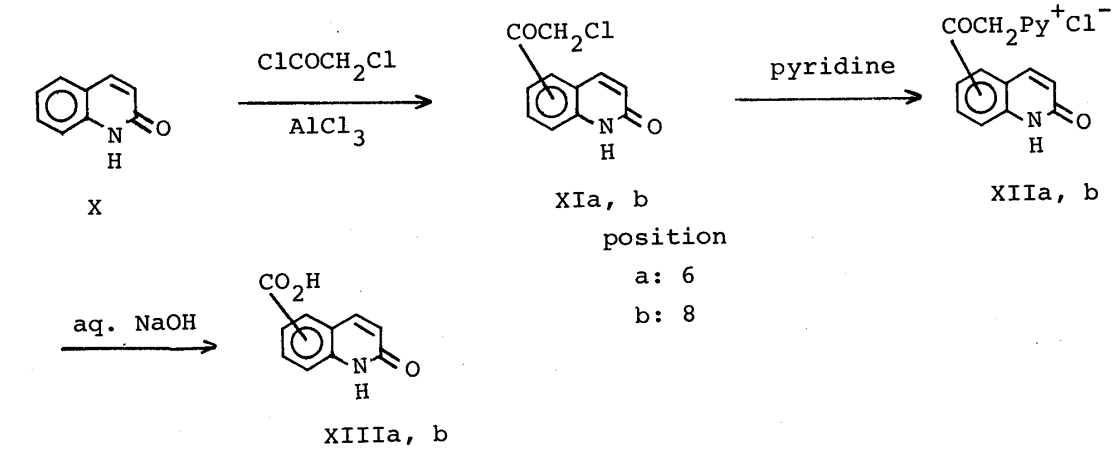
Chart 2

VI was achieved using sulfuric acid[5] 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 (^{1}H-NMR) spectrum, the spin-spin coupling constants of aromatic protons showed that compound VII had three aromatic protons adjacent to each other. Morevoer the ^{1}H-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 chloride[6] (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 ^{1}H-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



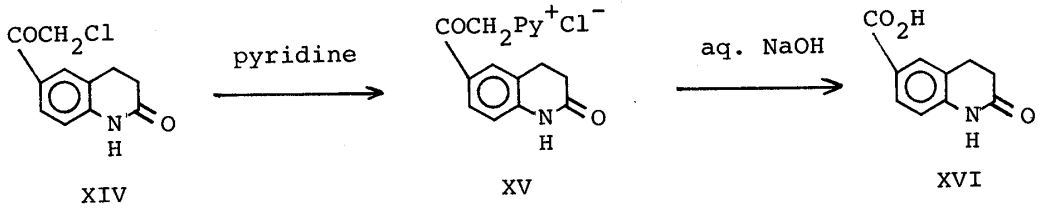


Chart 3

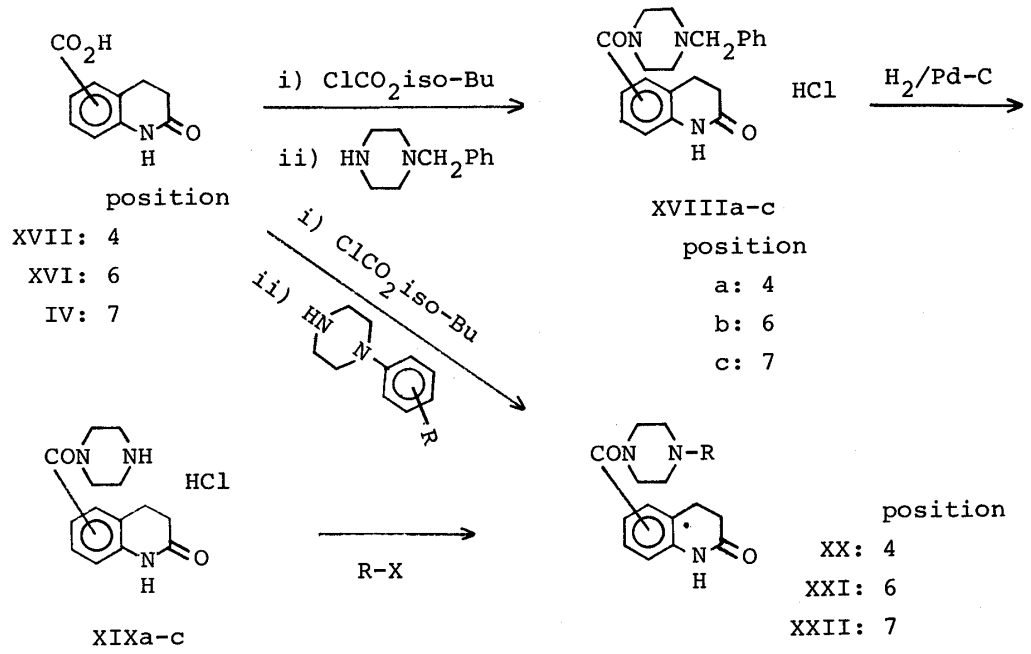


Chart 4

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 isobutyl 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(1*H*)-quinolinone derivatives (XX—XXII and XXVII—XXXI) were obtained in the usual manner using appropriate alkyl halides

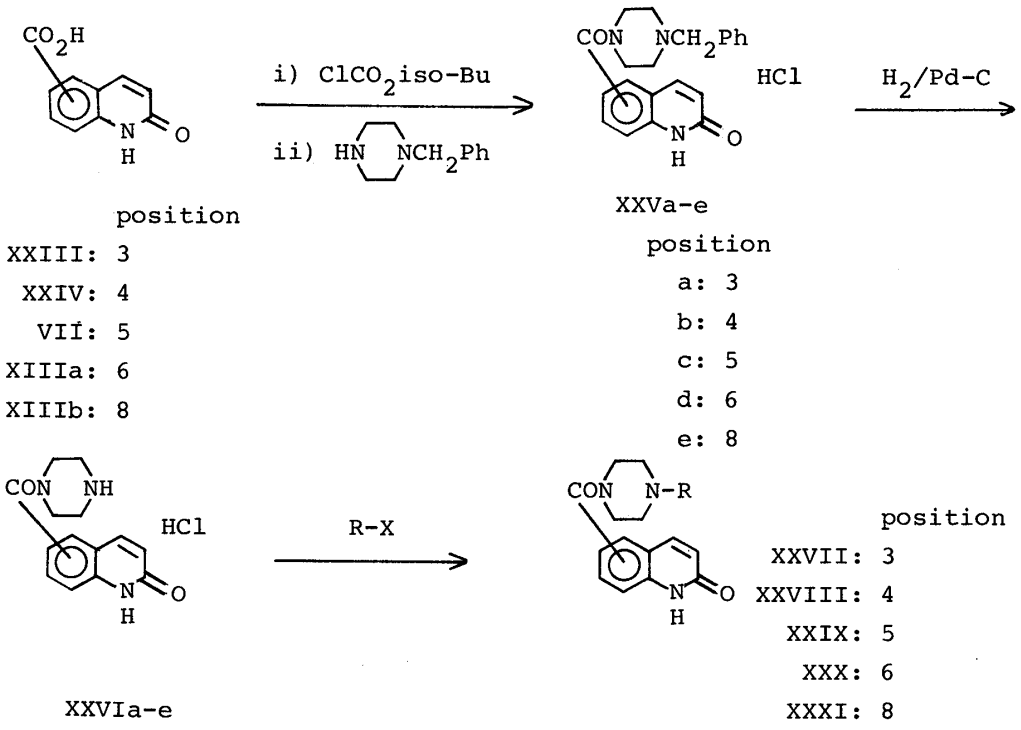
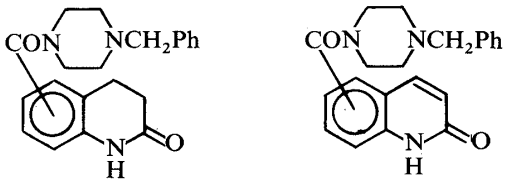


Chart 5

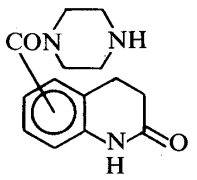
TABLE I. (4-Benzyl-1-piperazinylcarbonyl)-2(1*H*)-quinolinone Derivatives



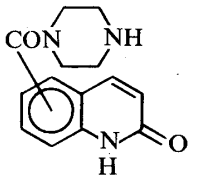
XVIIIa—c XXVa—e

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_2O	$C_{21}H_{23}N_3O_2 \cdot HCl \cdot 3/2\,H_2O$	61.08 (60.95	6.59 6.38	10.18 10.11)
XVIIIb	6	50	HCl	272—274	EtOH–H_2O	$C_{21}H_{23}N_3O_2 \cdot HCl$	65.36 (65.05	6.27 6.27	10.89 10.72)
XVIIIc	7	51	HCl	260—262	EtOH–H_2O	$C_{21}H_{23}N_3O_2 \cdot HCl$	65.36 (64.91	6.27 6.34	10.89 10.82)
XXVa	3	91	HCl	291—294 (dec.)	MeOH–H_2O	$C_{21}H_{21}N_3O_2 \cdot HCl$	65.70 (65.89	5.78 5.84	10.95 11.09)
XXVb	4	28	HCl	265—267 (dec.)	EtOH–H_2O	$C_{21}H_{21}N_3O_2 \cdot HCl \cdot 1/2\,H_2O$	64.20 (64.19	5.90 5.78	10.70 10.79)
XXVc	5	34	HCl	204—207	EtOH–H_2O	$C_{21}H_{21}N_3O_2 \cdot HCl \cdot 1/4\,H_2O$	64.95 (64.88	5.84 5.64	10.82 10.95)
XXVd	6	41	HCl	>300	EtOH–H_2O	$C_{21}H_{21}N_3O_2 \cdot HCl \cdot H_2O$	62.76 (62.57	6.02 6.29	10.46 10.55)
XXVe	8	49	HCl	177—180	EtOH	$C_{21}H_{21}N_3O_2 \cdot HCl \cdot 3/2\,H_2O$	61.39 (61.39	6.13 5.90	10.23 10.11)

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



XIXa—c



XXVIa—e

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_2O	$C_{14}H_{17}N_3O_2 \cdot HCl \cdot H_2O$	53.59 (53.70	6.42 6.41	13.39 13.64)
XIXb	6	91	HCl	>300	EtOH–H_2O	$C_{14}H_{17}N_3O_2 \cdot HCl$	56.85 (56.82	6.13 6.05	14.21 14.12)
XIXc	7	55	HCl	261.5—263	EtOH–H_2O	$C_{14}H_{17}N_3O_2 \cdot HCl$	56.85 (56.69	6.13 5.85	14.21 14.05)
XXVIa	3	93	HCl	>300	EtOH–H_2O	$C_{14}H_{15}N_3O_2 \cdot HCl \cdot 1/2\,H_2O$	55.54 (55.58	5.66 5.68	13.88 13.95)
XXVIb	4	95	HCl	>300	EtOH–H_2O	$C_{14}H_{15}N_3O_2 \cdot HCl \cdot H_2O$	53.93 (53.76	5.82 5.70	13.48 13.61)
XXVIc	5	96	HCl	>300	MeOH–H_2O	$C_{14}H_{15}N_3O_2 \cdot HCl \cdot H_2O$	53.93 (53.70	5.82 5.94	13.48 13.26)
XXVId	6	89	HCl	>300	EtOH–H_2O	$C_{14}H_{15}N_3O_2 \cdot HCl$	57.24 (57.03	5.49 5.47	14.31 14.33)
XXVIe	8	69	HCl	>300	EtOH–H_2O	$C_{14}H_{15}N_3O_2 \cdot HCl \cdot 1/4\,H_2O$	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.

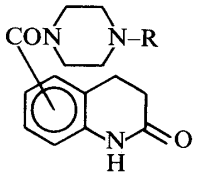
The *N*-substituents of the piperazine ring substantially affected the activity. The alkyl, benzoyl alkyl, phenoxy alkyl and phenyl alkyl derivatives showed high potency, whereas the benzoyl derivatives showed little activity. Among these compounds, XXIa, b, j, l, m, t, and XXVd showed greater positive inotropic activities than amrinone. Among them, compounds XXIj and XXIl showed little chronotropic activity. More detailed studies on compounds XXIj and XXIl 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)——$AlCl_3$ (122 g) was added portionwise to a suspension of

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



XX—XXII

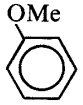
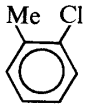
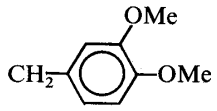
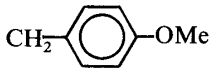
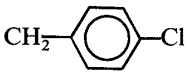
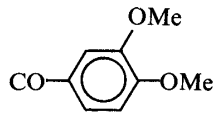
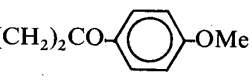
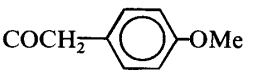
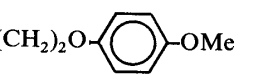
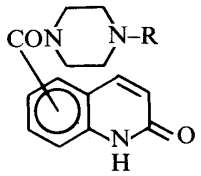
Compd. No.	Position	R	Yield (%)	Form	mp (°C)	Recrystn. solvent	Formula	Analysis (%) Calcd (Found) C	H	N
XXa	4	$(CH_2)_2COPh$	47	—	259—260 (dec.)	EtOH	$C_{23}H_{25}N_3O_3$	70.57 (70.68	6.44 6.50	10.74 10.63)
XXIa	6	Ph	17	—	200—201	iso-PrOH	$C_{20}H_{21}N_3O_2$	71.62 (71.63	6.31 6.22	12.53 12.58)
XXIb	6		47	—	226—227.5	EtOH–$CHCl_3$	$C_{21}H_{23}N_3O_3$	69.02 (69.06	6.34 6.26	11.50 11.38)
XXIc	6		19	—	210—211	MeOH	$C_{21}H_{22}ClN_3O_2$	65.70 (65.76	5.78 5.77	10.95 10.92)
XXId	6		33	HCl	240—242 (dec.)	MeOH–Et_2O	$C_{23}H_{27}N_3O_4 \cdot HCl \cdot 1/2H_2O$	60.72 (60.68	6.43 6.41	9.24 9.18)
XXIe	6		37	HCl	262—264 (dec.)	EtOH–H_2O	$C_{22}H_{25}N_3O_3 \cdot HCl$	63.53 (63.23	6.30 6.11	10.10 9.91)
XXIf	6		51	HCl	>300	EtOH–H_2O	$C_{21}H_{22}ClN_3O_2 \cdot HCl$	60.00 (60.29	5.52 5.51	10.00 10.12)
XXIg	6	$(CH_2)_2Ph$	49	HCl	269—272 (dec.)	MeOH	$C_{22}H_{25}N_3O_2 \cdot HCl \cdot 1/2H_2O$	64.62 (64.41	6.66 6.36	10.28 10.29)
XXIh	6		84	—	238—239.5	EtOH–$CHCl_3$	$C_{23}H_{25}N_3O_5$	65.23 (65.25	5.95 6.10	9.92 9.85)
XXIi	6	CH_2COPh	30	HCl	212—215	EtOH–H_2O	$C_{22}H_{23}N_3O_3 \cdot HCl \cdot 1/2H_2O$	62.48 (62.51	5.95 5.72	9.94 9.97)
XXIj	6	$(CH_2)_2COPh$	30	HCl	205—207 (dec.)	EtOH–H_2O	$C_{23}H_{25}N_3O_3 \cdot HCl$	64.55 (64.26	6.12 6.10	9.82 10.08)
XXIk	6		17	HCl	204—205 (dec.)	EtOH–H_2O	$C_{24}H_{27}N_3O_4 \cdot HCl \cdot H_2O$	60.56 (60.77	6.35 6.34	8.83 8.75)
XXIl	6	$(CH_2)_3COPh$	7.2	HCl	241—242.5	EtOH–H_2O	$C_{24}H_{27}N_3O_3 \cdot HCl \cdot 1/4H_2O$	64.56 (64.35	6.43 6.36	9.41 9.39)
XXIm	6	$(CH_2)_5COPh$	27	HCl	239—242	EtOH–H_2O	$C_{26}H_{31}N_3O_3 \cdot HCl \cdot H_2O$	63.99 (64.18	7.02 6.81	8.61 8.64)
XXIn	6		14	—	158—160	EtOH–Et_2O	$C_{23}H_{25}N_3O_4$	67.79 (67.72	6.18 6.17	10.31 10.27)
XXIo	6	CO_2Et	48	—	180—182	MeOH	$C_{17}H_{21}N_3O_4$	61.62 (61.38	6.39 6.31	12.68 12.61)
XXIp	6	$(CH_2)_2OPh$	44	HCl	271—274 (dec.)	EtOH–H_2O	$C_{22}H_{25}N_3O_3 \cdot HCl$	63.53 (63.23	6.30 6.18	10.10 9.97)
XXIq	6		20	HCl	270—272 (dec.)	EtOH–H_2O	$C_{23}H_{27}N_3O_4 \cdot HCl$	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	$(CH_2)_3OPh$	26	HCl	151—153 (dec.)	EtOH–H_2O	$C_{23}H_{27}N_3O_3 \cdot$ HCl	64.25 (64.05)	6.56 (6.58)	9.77 (9.72)
XXIs	6	*n*-Pr	26	HCl	259—262	EtOH	$C_{17}H_{23}N_3O_2 \cdot$ HCl$\cdot 1/2\,H_2O$	58.86 (58.85)	7.26 (7.18)	12.12 (12.31)
XXIt	6	iso-C_4H_9	47	HCl	292—293.5 (dec.)	MeOH–Et_2O	$C_{18}H_{25}N_3O_2 \cdot$ HCl	61.44 (61.28)	7.45 (7.15)	11.94 (11.81)
XXIIa	7	$(CH_2)_2COPh$	56	HCl	205—208 (dec.)	MeOH–H_2O	$C_{22}H_{25}N_3O_3 \cdot$ HCl$\cdot 1/2\,H_2O$	62.18 (62.47)	6.41 (6.52)	9.89 (9.62)
XXIIb	7	$(CH_2)_2OPh$	55	HCl	177—180	EtOH–H_2O	$C_{22}H_{25}N_3O_3 \cdot$ HCl	63.53 (63.42)	6.30 (6.43)	10.10 (10.11)

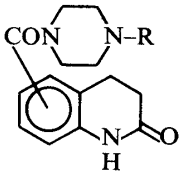
TABLE IV. (4-Substituted 1-piperazinylcarbonyl)-2(1*H*)-quinolinone Derivatives



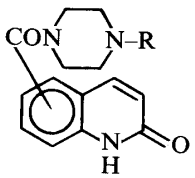
XXVII—XXXI

Compd. No.	Position	R	Yield (%)	Form	mp (°C)	Recrystn. solvent	Formula	Analysis (%) Calcd (Found) C	H	N
XXVIIa	3	$(CH_2)_2OPh$	13	HCl	280—282.5 (dec.)	MeOH	$C_{22}H_{23}N_3O_3 \cdot$ HCl	63.84 (63.66)	5.85 (5.85)	10.15 (10.10)
XXVIIb	3	iso-C_4H_9	1.7	HCl	281—282 (dec.)	EtOH–H_2O	$C_{18}H_{23}N_3O_2 \cdot$ HCl$\cdot 1/2\,H_2O$	60.24 (60.52)	7.02 (6.75)	11.71 (11.47)
XXVIIIa	4	$(CH_2)_2COPh$	22	HCl	207—209 (dec.)	MeOH–H_2O	$C_{23}H_{23}N_3O_3 \cdot$ HCl$\cdot 1/4\,H_2O$	64.18 (64.07)	5.74 (5.54)	9.76 (9.67)
XXVIIIb	4	iso-C_4H_9	14	HCl	278—281.5 (dec.)	MeOH	$C_{18}H_{23}N_3O_2 \cdot$ HCl$\cdot 3/2\,H_2O$	57.36 (57.58)	7.22 (6.95)	11.15 (11.27)
XXVIIIc	4	$(CH_2)_2OPh$	31	HCl	255.5—257 (dec.)	EtOH–H_2O	$C_{22}H_{23}N_3O_3 \cdot$ HCl$\cdot H_2O$	61.18 (61.00)	6.07 (5.88)	9.73 (9.82)
XXIXa	5	iso-C_4H_9	42	HCl	251—254 (dec.)	MeOH	$C_{18}H_{23}N_3O_2 \cdot$ HCl$\cdot 1/2\,H_2O$	60.25 (60.29)	7.02 (6.93)	11.71 (11.70)
XXIXb	5	$(CH_2)_2OPh$	50	HCl	227—229	iso-PrOH	$C_{22}H_{23}N_3O_3 \cdot$ HCl	63.84 (63.93)	5.85 (5.97)	10.15 (10.17)
XXIXc	5	$(CH_2)_2COPh$	12	HCl	181.5—184	EtOH	$C_{23}H_{23}N_3O_3 \cdot$ HCl$\cdot 3/4\,H_2O$	62.86 (62.86)	5.85 (5.66)	9.56 (9.53)
XXXa	6	$(CH_2)_2OPh$	60	HCl	286—289 (dec.)	EtOH–H_2O	$C_{22}H_{23}N_3O_3 \cdot$ HCl	63.83 (63.84)	5.85 (5.80)	10.15 (10.21)
XXXb	6	iso-C_4H_9	16	HCl	>300	MeOH	$C_{18}H_{23}N_3O_2 \cdot$ HCl$\cdot 1/2\,H_2O$	60.24 (60.44)	7.02 (6.87)	11.71 (11.89)
XXXc	6	$(CH_2)_3Ph$	21	HCl	290—293 (dec.)	EtOH–H_2O	$C_{23}H_{25}N_3O_2 \cdot$ HCl	67.06 (66.84)	6.36 (6.29)	10.20 (10.24)
XXXia	8	$(CH_2)_2COPh$	38	HCl	182—184	MeOH	$C_{23}H_{23}N_3O_3 \cdot$ HCl	64.86 (64.80)	5.68 (5.67)	9.87 (9.85)
XXXIb	8	iso-C_4H_9	7	HCl	284—288 (dec.)	MeOH	$C_{18}H_{23}N_3O_2 \cdot$ HCl$\cdot 1/4\,H_2O$	61.01 (61.13)	6.97 (6.79)	11.86 (12.16)

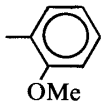
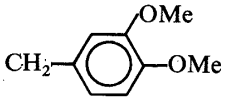
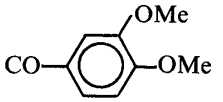
TABLE V. Biological Activity of 2(1*H*)-quinolinone Derivatives on the Canine Heart ($n=1$)



XVIII, XX, XXI, XXII



XXV, XXVII, XXIX, XXXI

Compd. No.	Position	R	Inotropic effect	Chronotropic effect
XVIIIb	6	CH_2Ph	1.0	LE
XXa	4	$(CH_2)_2COPh$	LE	LE
XXIa	6	Ph	5.4	3.4
XXIb	6		1.8	0.8
XXId	6		0.3	LE
XXIg	6	$(CH_2)_2Ph$	1.0	3.3
XXIh	6		0.2	0.2
XXIj	6	$(CH_2)_2COPh$	3.9	LE
XXIl	6	$(CH_2)_3COPh$	1.7	LE
XXIm	6	$(CH_2)_5COPh$	1.1	LE
XXIp	6	$(CH_2)_2OPh$	0.9	LE
XXIt	6	iso-C_4H_9	1.8	0.1
XXIIa	7	$(CH_2)_2COPh$	LE	LE
XXVd	6	CH_2Ph	1.3	2.8
XXVIIb	3	iso-C_4H_9	LE	LE
XXIXc	5	$(CH_2)_2COPh$	LE	LE
XXXIa	8	$(CH_2)_2COPh$	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 μmol) 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 CH_2Cl_2 (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 $CHCl_3$. The extract was washed with H_2O, dried (Na_2SO_4) 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 ν_{max}^{KBr} cm^{-1}: 1730, 1695, 1605. NMR ($CDCl_3$) δ: 2.51—3.18 (4H, m, $C\underline{H}_2C\underline{H}_2COO$), 3.67 (3H, s, $COOC\underline{H}_3$), 4.68 (2H, s, $COC\underline{H}_2Cl$), 7.32 (2H, d, $J=12$ Hz, aromatic H), 7.88 (2H, d, $J=12$ Hz, aromatic H). *Anal.* Calcd for $C_{12}H_{13}ClO_3$: C, 59.88; H, 5.44. Found: C, 59.64; H, 5.41.

4-(2-Methoxycarbonylethyl)-3-nitrobenzoic Acid (III)——Fuming HNO_3 (20.9 g, $d=1.52$) was added dropwise to a solution of II (36.3 g) in conc. H_2SO_4 (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 $CHCl_3$. The extract was washed with water, dried (Na_2SO_4) 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 ν_{max}^{KBr} cm^{-1}: 3100, 1735, 1685, 1615, 1530. NMR (DMSO-d_6) δ: 2.74 (2H, t, $J=7$ Hz, $C\underline{H}_2$), 3.17 (2H, t, $J=7$ Hz, $C\underline{H}_2$), 3.60 (3H, s, $OC\underline{H}_3$), 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, $COO\underline{H}$). *Anal.* Calcd for $C_{11}H_{11}NO_6$:

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 °C. IR ν_{max}^{KBr} cm^{-1}: 3270, 1695, 1635, 1585, 1390. NMR (DMSO-d_6) δ: 2.42—2.54, 2.89—3.01 (each 2H, m, $-CH_2CH_2-$), 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 $C_{10}H_9NO_3$: 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—202 °C. IR ν_{max}^{KBr} 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 $C_{12}H_{13}NO_4$: 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—50 °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—279 °C. IR ν_{max}^{KBr} 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 s, CONH), 13.10 (1H, br, COOH). *Anal.* Calcd for $C_{10}H_7NO_3$: 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—311 °C. IR ν_{max}^{KBr} cm^{-1}: 3070, 2660, 1685, 1650 (sh), 1590. NMR (DMSO-d_6) δ: 2.27—2.62, 2.91—3.51 (each 2H, m, CH_2CH_2CONH), 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 $C_{10}H_9NO_3$: C, 62.82; H, 4.75; N, 7.33. Found: C, 62.80; H, 4.77; N, 7.17.

6-Chloroacetyl-2(1*H*)-quinolinone (XIa) and 8-Chloroacetyl-2(1*H*)-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(1*H*)-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—277 °C (dec.). IR ν_{max}^{KBr} 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 s, CONH). *Anal.* Calcd for $C_{11}H_8ClNO_2$: C, 59.61; H, 3.64; N, 6.32. Found: C, 59.47; H, 3.63; N, 6.33.

XIb: mp 177.5—179 °C. IR ν_{max}^{KBr} 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 s, CONH). *Anal.* Calcd for $C_{11}H_8ClNO_2$: 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—90 °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 °C. IR ν_{max}^{KBr} 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: $C_{16}H_{13}ClN_2O_2 \cdot 1/2H_2O$: 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—264 °C (dec.). IR ν_{max}^{KBr} 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 $C_{16}H_{13}ClN_2O_2 \cdot 1/2H_2O$: 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–H_2O to give colorless needles mp 294—295 °C (dec.). IR ν_{max}^{KBr} cm^{-1}: 3550, 3400, 1670 (sh), 1635. NMR (DMSO-d_6 + D_2O) δ: 2.39—3.25 (4H, m, CH_2CH_2), 4.36 (2H, s, $COCH_2N$), 7.07 (1H, d, J=9 Hz, C_8-aromatic H), 7.77—9.02 (7H, m, aromatic H). *Anal.* Calcd for $C_{16}H_{15}ClN_2O_2$: 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 H_2O (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 ν_{max}^{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, C_8-aromatic H), 8.04 (1H, dd, J_1=8 Hz, J_2=2 Hz, C_7-aromatic H), 8.06 (1H, d, J=9 Hz, COCH=CH), 8.32 (1H, d, J=2 Hz, C_5-aromatic H), 12.07 (1H, br s, NHCO), 14.10 (1H, br, COOH). *Anal.* Calcd for $C_{10}H_7NO_3$: 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–$CHCl_3$ to give colorless needles, mp >300 °C. IR ν_{max}^{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, C_6-aromatic H), 8.01, 8.22 (each 1H, dd, J_1=8 Hz, J_2=1.5 Hz, C_5-, C_7-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 $C_{10}H_7NO_3$: 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 ν_{max}^{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, CH_2CH_2), 6.93 (1H, d, J=9 Hz, C_8-aromatic H), 7.75 (1H, dd, J_1=9 Hz, J_2=1.5 Hz, C_7-aromatic H), 7.78 (1H, s, C_5-aromatic H), 10.40 (1H, s, CONH), 12.29 (1H, br, COOH). *Anal.* Calcd for $C_{10}H_9NO_3$: 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(1*H*)-quinolinone Derivatives (XVIIIa—c, XXVa—e). 6-(4-Benzyl-1-piperazinylcarbonyl)-3,4-dihydro-2(1*H*)-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 Et_3N (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 $CHCl_3$, and the extract was washed with water, dried (Na_2SO_4) and concentrated *in vacuo*. The residue was treated with MeOH containing HCl, and concentrated *in vacuo*. The residue was recrystallized from EtOH–H_2O to give XVIIIb (31.3 g, 50%) as colorless needles, mp 272—274 °C (dec.). IR ν_{max}^{KBr} cm^{-1}: 3070, 2560, 1690, 1665, 1650. NMR (DMSO-d_6) δ: 2.27—4.52 (14H, m, $COCH_2CH_2$, $-N(CH_2CH_2)_2N-$, $N-CH_2-C_6H_5$), 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(1*H*)-quinolinone Derivatives (XIXa—c, XXVIa—e). 3,4-Dihydro-6-(1-piperazinylcarbonyl)-2(1*H*)-quinolinone (XIXb)——A mixture of XVIIIb (20 g) and 10% palladium on charcoal (2 g) in EtOH (130 ml) and H_2O (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–H_2O to give XIXb (14 g, 91%) as colorless scales, mp >300 °C. IR ν_{max}^{KBr} cm^{-1}: 3170, 3060, 2470, 1680, 1660. NMR (DMSO-d_6) δ: 2.22—3.93 (12H, $COCH_2CH_2$, $-N(CH_2CH_2)_2N-$), 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(1*H*)-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 Et_3N (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 $CHCl_3$. The extract was washed with water, dried (Na_2SO_4) 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 ν_{max}^{KBr} cm^{-1}: 1695, 1615, 1590, 1460, 1000. NMR (DMSO-d_6) δ: 2.15—3.09, 3.43—3.82 (12H, m, $COCH_2CH_2$, $-N(CH_2CH_2)_2N-$), 2.32 (3H, s, CH_3), 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(1*H*)-quinolinone (XXIf)——A suspension of XIXb (3.0 g), Et_3N (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–H_2O to give XXIf (2.5 g, 51%) as colorless needles, mp > 300 °C. IR ν_{max}^{KBr} cm^{-1}: 3070, 2400, 1690, 1660, 1655. NMR (DMSO-d_6) δ: 2.19—4.60 (14H, m, $-N(CH_2CH_2)_2N-$, $N-CH_2$, $NHCOCH_2CH_2$), 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 XXIh, n, o. 6-[4-(3,4-Dimethoxybenzoyl)-1-piperazinylcarbonyl]-3,4-dihydro-2(1*H*)-quinolinone (XXIh)——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 XXIh. (3.6 g, 84%) as colorless prisms, mp 238—239.5 °C. IR ν_{max}^{KBr} cm^{-1}: 3240, 1710, 1685 (sh), 1680, 1625. NMR ($CDCl_3$) δ: 2.51—3.19 (4H, m, $NHCOCH_2CH_2$), 3.63 (8H, s, $-N(CH_2CH_2)_2N-$, 3.87 (6H, s, $2\times OCH_3$), 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 XXIh and the yields, melting points and elemental analysis data are shown in Table III.

Preparation of XXa, XXIj—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(1*H*)-quinolinone (XXIj)——A mixture of β-chloropropiophenone (5.5 g) and NaI (6 g) in DMF (100 ml) was stirred at 50—55 °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—80 °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–H_2O to give XXIj (3.33 g, 29%) as colorless scales, mp 205—207 °C (dec.). IR ν_{max}^{KBr} cm^{-1}: 2570, 1675, 1645, 1615, 1595. NMR (DMSO-d_6) δ: 2.18—4.52 (16H, m, $-N(CH_2CH_2)_2N-$, $NHCOCH_2CH_2$, $N-CH_2CH_2CO$), 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 XXIj, 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 cardiotachometer (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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