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Studies on Positive Inotropic Agents. I. Synthesis of 3,4-Dihydro-6-[4-(3,4-dimethoxybenzoyl)-1-piperazinyl]-2(1*H*)-quinolinone and Related Compounds

Michiaki Tominaga,* Eiyu Yo, Hidenori Ogawa, Shuji Yamashita, Youichi Yabuuchi and Kazuyuki Nakagawa

Tokushima Research Institute, Otsuka Pharmaceutical Co., Ltd., Kagasuno 463–10, Kawauchi-cho, Tokushima-shi, 771–10, Japan

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Many (1-piperazinyl)-2(1*H*)-quinolinone derivatives were synthesized and examined for positive inotropic activities on the canine heart. Among them, 3,4-dihydro-6-[4-(3,4-dimethoxybenzoyl)-1-piperazinyl]-2(1*H*)-quinolinone (XVIIb-1) was found to have a very potent activity.

Keywords——congestive heart failure; positive inotropic agent; intramolecular aldol condensation; 3,4-dihydro-6-[4-(3,4-dimethoxybenzoyl)-1-piperazinyl]-2(1*H*)-quinolinone; biological activity

Cardiac glycosides have had an important role in the treatment of congestive heart failure for 200 years. However, they have a narrow therapeutic dose range.[1] Other positive inotropic agents, catecholamines, also have severe adverse effects such as tachycardia and arrythmia, and their route of clinical application is limited to intravenous injection.[2] Thus, it is desirable to find compounds having a potent positive inotropic effect with little chronotropic effect. Previously, we found that 5-(3-*tert*-butylamino-2-hydroxypropoxy)-3,4-dihydro-8-hydroxy-2(1*H*)-quinolinone (8-hydroxy carteolol) increased both cardiac contractile force and heart rate.[3] Therefore, we synthesized many 2(1*H*)-quinolinone derivatives and examined their effects on the canine heart. Some compounds were found to have a potent positive inotropic activity with little chronotropic effect. Herein, we report the synthesis and biological activities of various (1-piperazinyl)-2(1*H*)-quinolinone derivatives.

Synthesis

Many (1-piperazinyl)-2(1*H*)-quinolinone derivatives which have a substituted piperazine at the 3-, 4-, 5-, 6-, 7-, or 8-position of the 2(1*H*)-quinolinone skeleton were synthesized by three different procedures.

First, 3-(1-piperazinyl)-2(1*H*)-quinolinone derivatives were prepared by a route involving intramolecular aldol condensation as the key step (Chart 1). Reaction of *o*-chloroacetylaminobenzaldehyde dimethyl acetal (I)[4] with 1-benzylpiperazine in the presence of triethylamine, followed by treatment with hydrochloric acid, gave the key intermediate 2-(4-benzyl-1-piperazinylacetylamino)benzaldehyde dihydrochloride (II) in 82% yield. Intramolecular aldol condensation of II was achieved by using EtONa in EtOH under reflux to give 3-(4-benzyl-1-piperazinyl)-2(1*H*)-quinolinone hydrochloride (III) in 42% yield. Hydrogenolysis of III over 5% palladium on charcoal gave 3-(1-piperazinyl)-2(1*H*)-quinolinone hydrochloride (IV) in 85% yield. 3-(4-Substituted 1-piperazinyl)-2(1*H*)-quinolinone derivatives (Va, b) were obtained from IV in the usual manner by using β-chloropropio-

phenone or 3,4-dimethoxybenzoyl chloride (Table I).

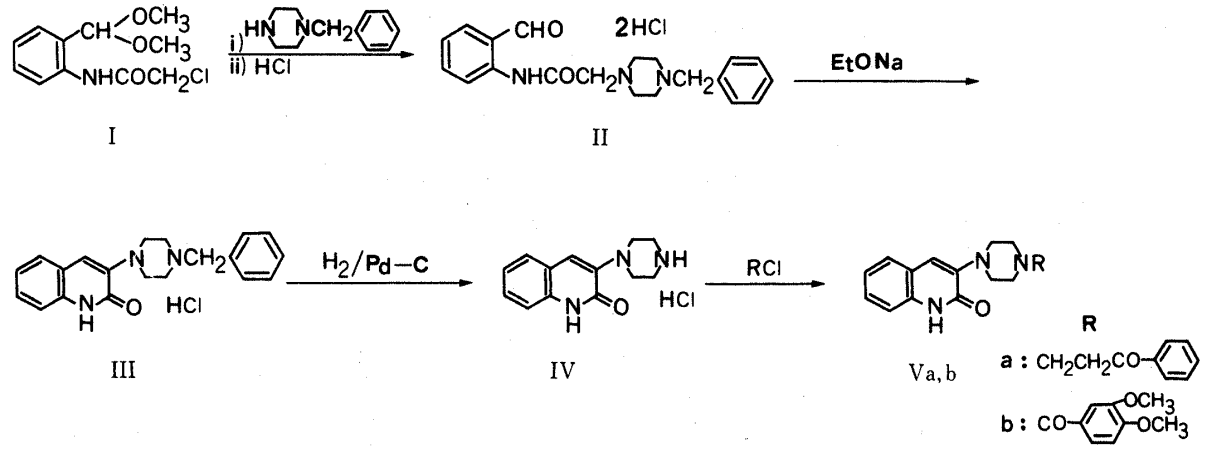


Chart 1

Secondly, 4-(4-substituted 1-piperazinyl)-2(1*H*)-quinolinone derivatives (IXa—d) were synthesized through the nucleophilic substitution reaction of 1-benzylpiperazine with 4-chloro-2(1*H*)-quinolinone (VI)[5] (Chart 2). Treatment of VI with excess 1-benzylpiperazine at 120—130 °C in hexamethylphosphoric triamide gave 4-(4-benzyl-1-piperazinyl)-2(1*H*)-quinolinone hydrochloride (VII) in 91% yield. Hydrogenolysis of VII over 5% palladium on charcoal gave 4-(1-piperazinyl)-2(1*H*)-quinolinone hydrochloride (VIII) in 90% yield. Compounds IXa—d were prepared from VIII in the same manner as described for the synthesis of V (Table I).

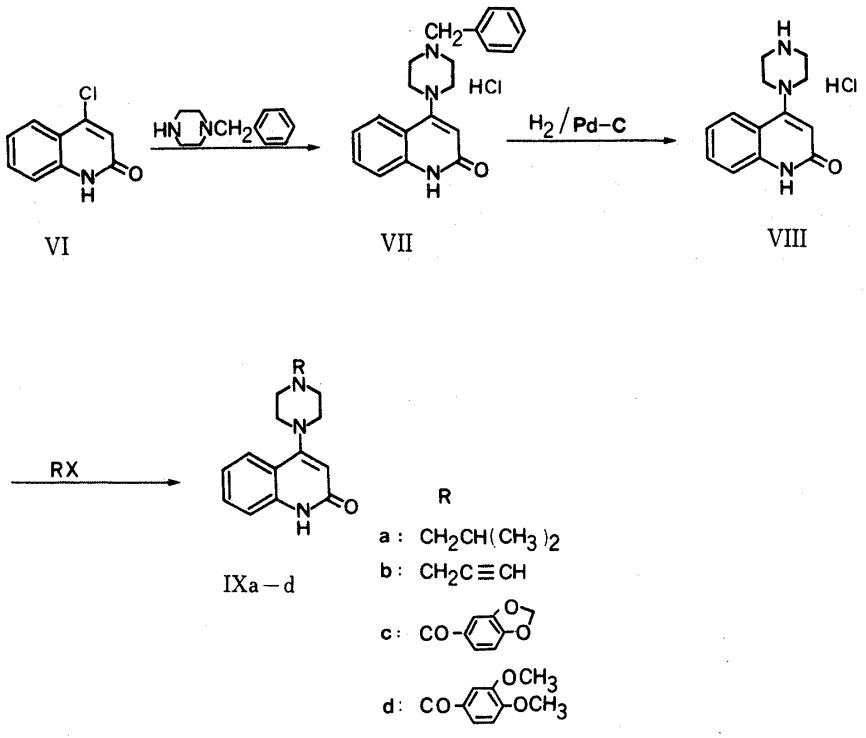


Chart 2

Thirdly, 5-, 6-, 7-, and 8-(4-substituted 1-piperazinyl)-3,4-dihydro-2(1*H*)-quinolinone derivatives (XVII) were obtained through the piperazine ring formation method[6] from bis(*β*-

bromoethyl)amine hydrobromide[7] and 5-,[8] 6-,[9] 7-,[10] and 8-amino-3,4-dihydro-2(1*H*)-quinolinone (XVa—d) (Chart 4). A preparation of 8-amino-2(1*H*)-quinolinone[11] (XIVb) has already been reported, but the method did not give a satisfactory yield. We, therefore, synthesized XIVb and its dihydro derivative (XVd) using the ring closure reaction of *o*-acetylamino-*β*-ethoxyacryloanilide (XI) (Chart 3). *o*-Acetylaminoaniline (X) was converted to XI (78%) by treatment with *β*-ethoxyacryloyl chloride,[12] then cyclized in the presence of sulfuric acid[13] to give 8-acetylamino-2(1*H*)-quinolinone (XII) in 72% yield. Hydrogenation of XII over 10% palladium on charcoal gave 8-acetylamino-3,4-dihydro-2(1*H*)-quinolinone (XIII) in 94% yield. Hydrolysis of XII and XIII gave 8-amino-2(1*H*)-quinolinone (XIVb) (91%) and 8-amino-3,4-dihydro-2(1*H*)-quinolinone hydrochloride (XVd) (84%), respectively.

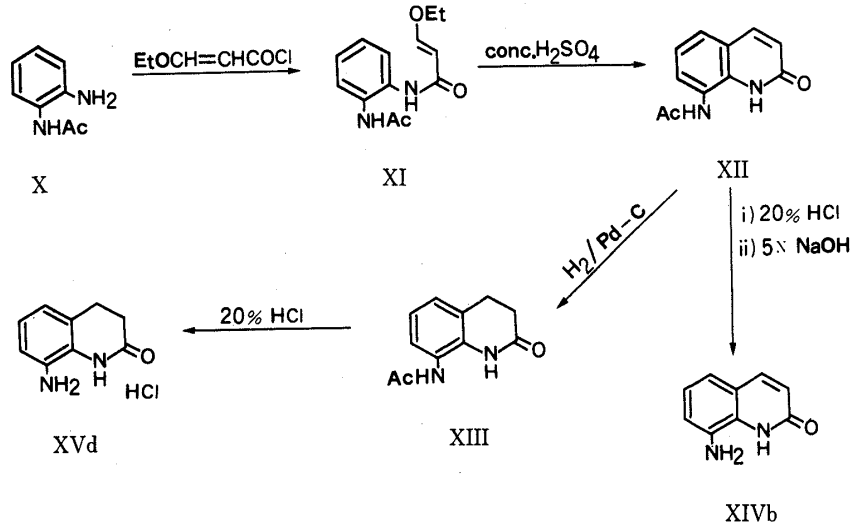


Chart 3

Treatment of XVa—c and the free base of XVd with an equivalent amount of bis(*β*-bromoethyl)amine hydrobromide in refluxing EtOH, followed by the addition of sodium carbonate and further heating, gave 3,4-dihydro-(1-piperazinyl)-2(1*H*)-quinolinones (XVIa—d) (Table II). Derivatives of 3,4-dihydro-(4-substituted 1-piperazinyl)-2(1*H*)-quinolinone (XVII) were obtained from XVIa—d in the same manner as described for the synthesis of V (Chart 4, Table III).

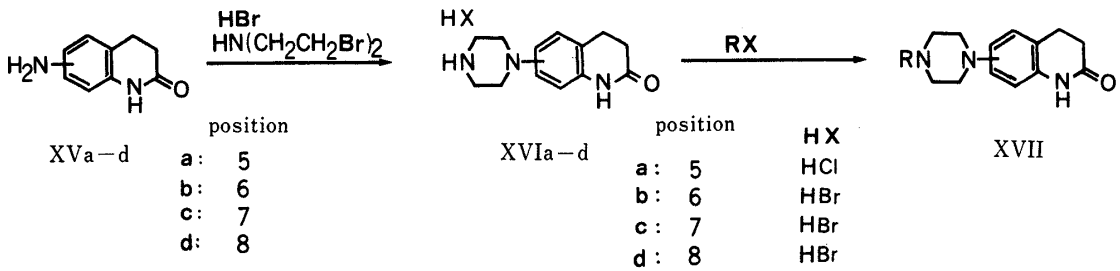


Chart 4

Derivatives of 6- and 8-(4-substituted 1-piperazinyl)-2(1*H*)-quinolinone (XIX) were prepared from 6-[14] and 8-amino-2(1*H*)-quinolinone (XIVa, b), respectively, in the same manner as described for the synthesis of XVII (Chart 5, Table I).

1-Alkyl-3,4-dihydro-6-[4-(3,4-dimethoxybenzoyl)-1-piperazinyl-[2(1*H*)-quinolinones (XXa, b) were obtained from 3,4-dihydro-6-[4-(3,4-dimethoxybenzoyl)-1-piperazinyl]-2(1*H*)-

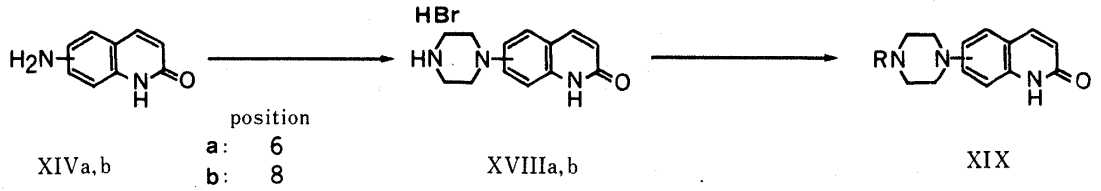


Chart 5

quinolinone (XVIIb-1) with alkyl halides in the presence of NaH in DMF in the usual manner (Chart 6, Table III).

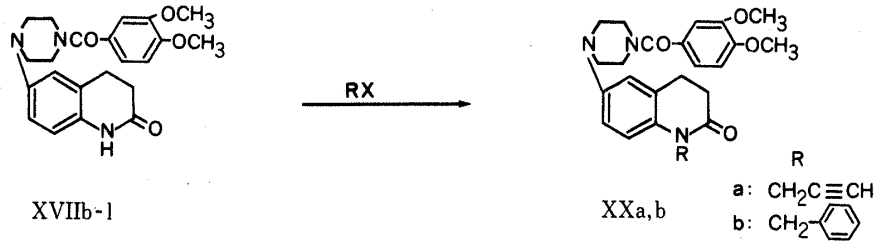


Chart 6

3,4-Dihydro-6-[4-(3,4-dimethoxybenzoyl)-1-piperazinyl]-8-methoxy-2(1*H*)-quinolinone (XXVI) was obtained from 3,4-dihydro-8-hydroxy-2(1*H*)-quinolinone (XXI)[15] according to the procedure shown in Chart 7. Treatment of compound XXI with acetic anhydride, followed by nitric acid gave 8-acetoxy-3,4-dihydro-6-nitro-2(1*H*)-quinolinone (XXII) in 85% yield. Methylation of XXII with methyl iodide gave 3,4-dihydro-8-methoxy-6-nitro-2(1*H*)-quinolinone (XXIII) in 75% yield. Hydrogenation of XXIII over 5% palladium on charcoal gave 6-amino-3,4-dihydro-8-methoxy-2(1*H*)-quinolinone (XXIV) in 86% yield. Compound XXVI was prepared from XXIV in the same manner as described for the synthesis of XVII (Table III).

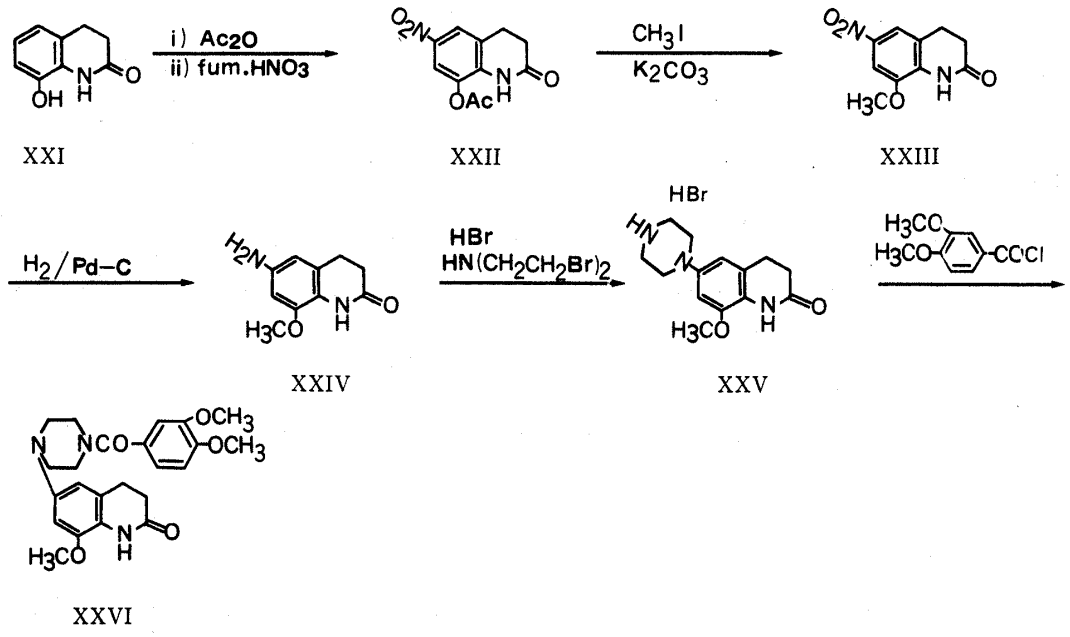
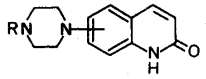


Chart 7

TABLE I. (4-Substituted 1-Piperazinyl)-2(1*H*)-quinolinone Derivatives



Va, b, IXa—d, XIX

Compd. No.	Position	R	Acid salt	Yield (%)	mp (°C)	Recrystn. solvent	Formula	Analysis (%) Calcd (Found) C	H	N
Va	3	CH_2CH_2CO-Ph	HCl	48	215—216	EtOH–H_2O	$C_{22}H_{23}N_3O_2 \cdot HCl$	66.41 (66.46)	6.08 6.26	10.56 10.49)
Vb	3	CO-(2,5-dimethoxyphenyl)	—	45	206—209	EtOH	$C_{22}H_{23}N_3O_4$	67.16 (67.15)	5.89 5.95	10.68 10.42)
IXa	4	$CH_2CH(CH_3)_2$	HCl	28	295—297 (dec.)	EtOH	$C_{17}H_{23}N_3O_4 \cdot HCl \cdot H_2O$	60.08 (59.82)	7.71 7.50	12.37 12.33)
IXb	4	$CH_2C{\equiv}CH$	HCl	48	242—244 (dec.)	EtOH	$C_{16}H_{17}N_3O \cdot HCl \cdot H_2O$	59.71 (59.65)	6.26 6.40	13.06 13.29)
IXc	4	CO-(1,3-benzodioxol-5-yl)	—	32	159—160.5	EtOH–$CHCl_3$	$C_{21}H_{19}N_3O_4$	66.83 (66.78)	5.07 5.21	11.14 11.15)
IXd	4	CO-(3,4-dimethoxyphenyl)	—	46	158—159	EtOH–$CHCl_3$	$C_{22}H_{23}N_3O_4$	67.16 (66.91)	5.89 5.88	10.68 10.54)
XIXa-1	6	CO-(3,4-dimethoxyphenyl)	—	50	265—266.5	MeOH–$CHCl_3$	$C_{22}H_{23}N_3O_4$	67.16 (67.14)	5.89 6.04	10.68 10.58)
XIXa-2	6	CO-(4-cyanophenyl)	—	58	300—301 (dec.)	EtOH–$CHCl_3$	$C_{21}H_{18}N_4O_2$	70.37 (70.35)	5.06 5.14	15.63 15.74)
XIXa-3	6	CO-(1,3-benzodioxol-5-yl)	—	49	266—267	MeOH–$CHCl_3$	$C_{21}H_{19}N_3O_4$	66.83 (66.79)	5.07 5.21	11.14 11.14)
XIXa-4	6	CO-Ph	—	46	264—265	EtOH–$CHCl_3$	$C_{20}H_{19}N_3O_2$	72.05 (72.08)	5.74 5.77	12.61 12.73)
XIXa-5	6	CO-(3-pyridyl)	—	20	250—252	EtOH	$C_{19}H_{18}N_4O_2$	68.24 (68.30)	5.42 5.50	16.76 16.98)
XIXb-1	8	CO-(4-chlorophenyl)	—	29	255.5—257	EtOH–$CHCl_3$	$C_{20}H_{18}ClN_3O_2$	65.30 (65.49)	4.39 5.09	11.42 11.54)
XIXb-2	8	CO-(3,4-dimethoxyphenyl)	—	51	197—198	EtOH	$C_{22}H_{23}N_3O_4$	67.16 (66.93)	5.89 5.87	10.68 10.64)
XIXb-3	8	CO-Ph	—	61	244—245	EtOH	$C_{20}H_{19}N_3O_2$	72.05 (72.18)	5.74 5.86	12.61 12.71)

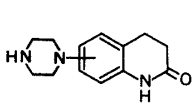
Biological Activity

Some of the (1-piperazinyl)-2(1*H*)-quinolinone derivatives which have relatively potent positive inotropic activities are listed in Table IV. The inotropic and chronotropic effects of these compounds were compared with those of amrinone.[16] Compounds XVIIa-2, b-1,4 and XIXa-1, 3, 5 showed greater positive inotropic activities than amrinone. Among them, compounds XVIIa-2, b-1, 4 showed little chronotropic activity and, in particular, compound XVIIb-1 (OPC-8212) showed the best profile as a potential drug for treatment of congestive heart failure. More detailed pharmacological and toxicological studies of OPC-8212 are in progress.

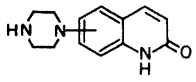
Experimental

All melting points are uncorrected. Infrared (IR) spectra were recorded on a JASCO IRA-2 spectrometer. Nuclear magnetic resonance (NMR) spectra were recorded on a Varian EM-390 NMR spectrometer using tetramethylsilane or 3-(trimethylsilyl)propionic acid-d_5 as an internal standard.

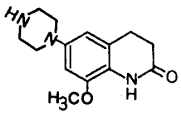
TABLE II. (1-Piperazinyl)-2(1*H*)-quinolinone Derivatives



XVIa—d



XVIIIa, b



XXV

Compd. No.	Position	Acid salt	Yield (%)	mp (°C)	Recrystn. solvent	Formula	Analysis (%) Calcd (Found)		
							C	H	N
XVIa	5	HCl	41	>300	MeOH	$C_{13}H_{17}N_3O \cdot HCl \cdot H_2O$	56.42	6.92	15.18
							(56.29	6.78	15.22)
XVIb	6	HBr	64	289—293 (dec.)	EtOH–H_2O	$C_{13}H_{17}N_3O \cdot HBr$	50.01	5.81	13.46
							(50.08	5.75	13.60)
XVIc	7	HBr	35	255—257 (dec.)	MeOH	$C_{13}H_{17}N_3O \cdot HBr$	50.01	5.81	13.46
							(49.87	5.74	13.46)
XVId	8	HBr	43	>300	EtOH	$C_{13}H_{17}N_3O \cdot HBr$	50.01	5.81	13.46
							(50.19	5.72	13.69)
XVIIIa	6	HBr	40	>300	EtOH–H_2O	$C_{13}H_{15}N_3O \cdot HBr$	50.34	5.20	13.55
							(50.29	5.22	13.63)
XVIIIb	8	HBr	32	>300	MeOH	$C_{13}H_{15}N_3O \cdot HBr \cdot H_2O$	48.92	5.37	13.17
							(48.91	5.26	13.13)
XXV	—	HBr	45	285—287 (dec.)	EtOH–H_2O	$C_{14}H_{19}N_3O_2 \cdot HBr$	49.13	5.89	12.28
							(48.92	5.80	12.27)

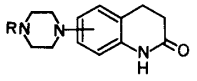
2-(4-Benzyl-1-piperazinylacetylamino)benzaldehyde Dihydrochloride (II)——A mixture of *o*-chloroacetylaminobenzaldehyde dimethyl acetal (I) (16.7 g), Et_3N (14.4 ml) and 1-benzylpiperazine (15.4 g) in acetonitrile (160 ml) was heated under reflux for 3 h. After cooling, the mixture was poured into dil. NaOH and extracted with $CHCl_3$. The $CHCl_3$ solution was washed with water and concentrated *in vacuo*. The residue was dissolved in MeOH–H_2O (100 ml, 1 : 1 mixture). The solution was acidified with conc. HCl to pH 1, then heated under reflux for 5 min. The reaction mixture was concentrated *in vacuo*. The residue was recrystallized from MeOH to give II (19.0 g, 82%) as colorless needles, mp 202—204 °C. IR ν_{max}^{KBr} cm^{-1}: 3320, 1702, 1676, 1618, 1595, 1201. NMR (DMSO-d_6) δ: 3.34 (8H, br s, $-N(CH_2CH_2)_2N-$), 3.80, 4.37 (each 2H, s, $-COCH_2N-$, $-CH_2C_6H_5$), 7.21—7.85 (7H, m, aromatic H). 7.92, 8.28 (each 1H, dd, $J_1=9$ Hz, $J_2=2$ Hz, aromatic H). 10.08 (1H, s, $-CHO$), 11.69 (1H, br s, $-NHCO-$). *Anal.* Calcd for $C_{20}H_{23}N_3O_2 \cdot 2HCl \cdot 1/2H_2O$: C, 57.28; H, 6.25; N, 10.02. Found: C, 57.18; H, 6.25; N, 10.21.

3-(4-Benzyl-1-piperazinyl)-2(1*H*)-quinolinone Hydrochloride (III)——An EtOH solution of EtONa was prepared from Na (4.6 g) and absolute EtOH (150 ml). II (9.7 g) was added to the solution, and the mixture was heated under reflux for 1 h. After cooling, the reaction mixture was poured into ice-water. The precipitates were collected by filtration, washed with water, and dissolved in MeOH containing HCl. The solution was concentrated *in vacuo* and the residue was recrystallized from MeOH to give III (3.9 g, 42%) as colorless needles, mp 294—296 °C (dec.). IR ν_{max}^{KBr} cm^{-1}: 3020, 2460, 1651, 1617, 1579, 1120. NMR (DMSO-d_6) δ: 2.26—2.77, 2.90—3.40 (each 4H, m, $-N(CH_2CH_2)_2N-$), 3.48 (2H, s, $-CH_2C_6H_5$), 6.83—7.67 (10H, m, aromatic H), 11.61 (1H, br s, $-NHCO-$). *Anal.* Calcd for $C_{20}H_{21}N_3O \cdot HCl$: C, 67.50; H, 6.23; N, 11.81. Found: C, 67.48; H, 6.15; N, 11.57.

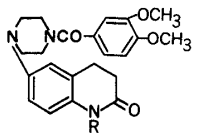
3-(1-Piperazinyl)-2(1*H*)-quinolinone Hydrochloride (IV)——A mixture of III (3.7 g) and 5% palladium on charcoal (0.4 g) in 60 ml of EtOH–H_2O (3 : 1 mixture) was stirred at 40—50 °C for 3 h under atmospheric pressure of hydrogen until the absorption of hydrogen ceased. The catalyst was filtered off and the filtrate was concentrated *in vacuo*. The residue was recrystallized from EtOH–H_2O to give IV (2.4 g, 85%) as colorless prisms, mp >300 °C. IR ν_{max}^{KBr} cm^{-1}: 3450, 1651, 1614, 1577, 1430, 1141. NMR (DMSO-d_6) δ: 2.88—3.63 (8H, m, $-N(CH_2CH_2)_2N-$), 6.85—7.67 (5H, m, aromatic H), 9.40 (2H, br s, 2 × $-NH-$). *Anal.* Calcd for $C_{13}H_{15}N_3O$: C, 58.75; H, 6.07; N, 15.81. Found: C, 58.46; H, 5.86; N, 15.57.

Preparation of (4-Alkyl-1-piperazinyl)-2(1*H*)-quinolinone Derivatives (Va, IXa, b, XVIIa-4, 5, b-8, 9). 3,4-Dihydro-6-[4-(4-methoxybenzyl)-1-piperazinyl]-2(1*H*)-quinolinone (XVIIb-8)——A mixture of 3,4-dihydro-6-(1-piperazinyl)-2(1*H*)-quinolinone hydrobromide (XVIb) (3.1 g, 0.010 mol), *p*-methoxybenzyl chloride (1.9 g, 0.012 mol) and K_2CO_3 (3.0 g, 0.022 mol) in DMF (20 ml) was stirred at 70—80 °C for 2.5 h. After cooling, the mixture was poured into ice-water and extracted with $CHCl_3$. The $CHCl_3$ solution was washed with water, dried (Na_2SO_4) and

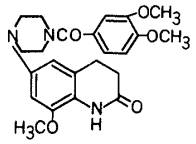
TABLE III. 3,4-Dihydro-(4-substituted 1-Piperazinyl)-2(1*H*)-quinolinone Derivatives



XVII



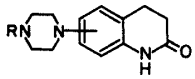
XXa, b



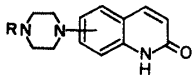
XXVI

Compd. No.	Position	R	Yield (%)	mp (°C)	Recrystn. solvent	Formula	Analysis (%) Calcd (Found) C	H	N
XVIIa-1	5	CO-(2,3-OCH3)	56	207—208	EtOH	$C_{22}H_{25}N_3O_4$	66.82 (66.76)	6.37 (6.47)	10.63 (10.66)
XVIIa-2	5	CO-(4-CN)	48	266—269	MeOH–$CHCl_3$	$C_{21}H_{20}N_4O_2$	69.98 (69.94)	5.59 (5.64)	15.55 (15.59)
XVIIa-3	5	CO-(4-NO_2)	57	292—294	MeOH–$CHCl_3$	$C_{20}H_{20}N_4O_4$	63.15 (63.19)	5.30 (5.39)	14.73 (14.98)
XVIIb-1	6	CO-(2,3-OCH3)	70	238—239.5	EtOH–$CHCl_3$	$C_{22}H_{25}N_3O_4$	66.82 (66.75)	6.37 (6.35)	10.63 (10.66)
XVIIb-2	6	CO-(4-OCH3)	35	216—218	MeOH	$C_{21}H_{23}N_3O_3$	69.02 (69.18)	6.34 (6.38)	11.50 (11.59)
XVIIb-3	6	CO-(4-Cl)	34	233—235	MeOH	$C_{20}H_{20}ClN_3O_2$	64.95 (64.76)	5.45 (5.51)	11.36 (11.37)
XVIIb-4	6	CO-(3,4-methylenedioxy)	37	191—193	MeOH	$C_{21}H_{21}N_3O_4$	66.48 (66.53)	5.58 (5.77)	11.08 (11.06)
XVIIb-5	6	CO-C6H5	67	221—225.5	EtOH	$C_{20}H_{21}N_2O_3$	71.62 (71.61)	6.31 (6.38)	12.53 (12.47)
XVIIb-6	6	$COCH_3$	40	203—205	iso-PrOH	$C_{15}H_{19}N_3O_2$	65.91 (65.79)	7.01 (6.97)	15.37 (15.29)
XVIIb-7	6	COCH=CH-(4-CH_3)	25	243—244.5	MeOH–$CHCl_3$	$C_{23}H_{25}N_3O_2$	73.57 (73.64)	6.71 (6.78)	11.19 (11.28)
XVIIc-1	7	CO-(3,4-methylenedioxy)	37	207—208	EtOH	$C_{21}H_{21}N_3O_4$	66.48 (66.52)	5.58 (5.62)	11.08 (11.13)
XVIIc-2	7	CO-(4-OCH3)	40	231—233	EtOH	$C_{21}H_{23}N_3O_3$	69.02 (69.30)	6.34 (6.43)	11.50 (11.61)
XVIIc-3	7	CO-C6H5	26	264.5—265.5	MeOH–$CHCl_3$	$C_{20}H_{21}N_3O_2$	71.62 (71.66)	6.31 (6.36)	12.53 (12.66)
XVIId-1	8	CO-(2,3-OCH3)	45	146—148	EtOH	$C_{22}H_{25}N_3O_4$	66.82 (66.60)	6.37 (6.43)	10.63 (10.51)
XVIId-2	8	CO-(3,4-methylenedioxy)	67	195—197	EtOH	$C_{21}H_{21}N_3O_4$	66.48 (66.43)	5.58 (5.64)	11.08 (10.97)
XVIIa-4	5	CH_2-(4-NO_2)	38	268—271	$CHCl_3$–Et_2O	$C_{20}H_{22}N_4O_3$	65.56 (65.49)	6.05 (5.92)	15.29 (15.16)
XVIIa-5	5	$CH_2C{\equiv}CH$	9	225—226	$CHCl_3$	$C_{16}H_{19}N_3O$	71.34 (71.31)	7.11 (7.11)	15.60 (15.60)
XVIIb-8	6	CH_2-(4-OCH_3)	60	196—198	EtOH	$C_{21}H_{25}N_3O_2$	71.77 (71.89)	7.17 (7.27)	11.96 (11.83)
XVIIb-9	6	CH_2-(4-Cl)	44	190—192	MeOH–$CHCl_3$	$C_{20}H_{22}ClN_3O$	67.51 (67.31)	6.23 (6.17)	11.81 (11.83)
XXa	—	$CH_2C{\equiv}CH$	32	152—154	EtOH	$C_{25}H_{27}N_3O_4$	69.26 (69.14)	6.28 (6.38)	9.69 (9.60)
XXb	—	CH_2-C6H5	45	131.5—132.5	EtOH	$C_{29}H_{31}N_3O_4 \cdot H_2O$	70.43 (70.60)	6.52 (6.45)	8.50 (8.46)
XXVI	—	CO-(2,3-OCH3)	65	162.5—163.5	iso-PrOH	$C_{23}H_{27}N_3O_5$	64.92 (65.09)	6.40 (6.55)	9.88 (9.69)

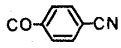
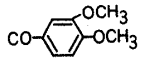
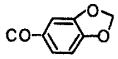
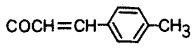
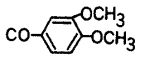
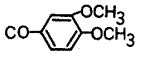
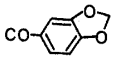
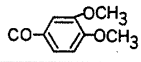
TABLE IV. Biological Activities of (1-Piperazinyl)-2(1*H*)-quinolinone Derivatives on the Canine Heart



XVII



VIII, XIX

Compd. No.	Position	R	Inotropic effect	Chronotropic effect
VIII	4	H	0.7	LE[a]
XVIIa-2	5		1.6	LE
XVIIb-1	6		1.8	LE
XVIIb-4	6		1.5	LE
XVIIb-5	6		0.7	0.3
XVIIb-7	6		0.7	LE
XVIId-1	8		0.7	LE
XIXa-1	6		3.8	0.8
XIXa-3	6		1.8	0.4
XIXa-5	6		1.8	0.5
XIXb-2	8		0.9	LE

The potencies of inotropic and chronotropic effects of the test compounds were evaluated at doses (ED 50%) producing the half-maximal response and expressed relative to those of amrinone as follows. Activity ratio of a test compound = ED 50% of amrinone/ED 50% of test compound. The larger the activity ratio, the more potent is the drug.
a) LE means little effect.

concentrated *in vacuo*. The residue was recrystallized from EtOH to give XVIIb-8 (2.1 g, 60%) as colorless needles, mp 196—198 °C. IR ν_{max}^{KBr} cm^{-1}: 3210, 3070, 1670, 1616, 1510, 1391, 1247. NMR ($CDCl_3$) δ: 2.35—3.26 (12H, m, $-CH_2CH_2-$, $-N(CH_2CH_2)_2$ N–), 3.41 (2H, s, $-CH_2C_6H_4-$), 3.70 (3H, s, $-OCH_3$), 6.62 (3H, s, C_5-, C_7-, C_8- aromatic H), 6.75, 7.13 (each 2H, d, J=9 Hz, $-C_6H_4OCH_3$), 9.02 (1H, s, $-NHCO-$). The elemental analysis data are given in Table III.

Compounds Va, IXa, b and XVIIa-4, 5, b-9 were obtained in the same manner as described for XVIIb-8. The yield, melting point and elemental analysis data are given in Table I and Table III.

Preparation of (4-Acyl-1-piperazinyl)-2(1*H*)-quinolinone Derivatives (Vb, IXc, d, XVIIa-1—3, b-1—7, c-1—3, d-1, 2, XIXa-1—5, b-1—3, XXVI). 3,4-Dihydro-6-[4-(3,4-dimethoxybenzoyl)-1-piperazinyl]-2(1*H*)-quinolinone (XVIIb-1)——A solution of 3,4-dimethoxybenzoyl chloride (2.2 g, 0.011 mol) in absolute DMF (10 ml) was added dropwise to a mixture of XVIb (3.1 g, 0.010 mol) and Et_3N (2.2 g, 0.022 mol) in absolute DMF (40 ml) with stirring and ice-cooling. After the addition, the mixture was stirred at room temperature for 1 h. The mixture was poured into ice-water and extracted with $CHCl_3$. The $CHCl_3$ solution was washed with water, dried (Na_2SO_4) and concentrated *in vacuo*. The residue was chromatographed over silica gel (eluent, $CHCl_3$–MeOH = 100 : 1), then recrystallized from EtOH–$CHCl_3$ to give XVIIb-1 (2.7 g, 70%) as colorless granular crystals, mp 238—239.5 °C. IR ν_{max}^{KBr} cm^{-1}: 3210, 3075, 1670, 1643, 1510, 1427, 1260, 1233. NMR ($CDCl_3$) δ: 2.40—3.25 (8H, m, $-CH_2CH_2-$, $-N(CH_2CH_2)_2NCO-$), 3.55—3.98 [10H, m, 3.87 (6H, s, 2×$-OCH_3$), $-CON(CH_2CH_2)_2N-$] 6.61—7.12 (6H, m, aromatic H), 9.02 (1H, s, $-NHCO-$). The elemental analysis data are given in Table III.

Compounds Vb, IXc, d, XVIIa-1—3, b-2—7, c-1—3, d-1,2, XIXa-1—5, b-1—3 and XXVI were obtained in the same manner as described for XVIIb-1, and the yield, melting point and elemental analysis data are given in Table I and Table III.

4-(4-Benzyl-1-piperazinyl)-2(1*H*)-quinolinone Hydrochloride (VII)——A solution of 4-chloro-2(1*H*)-quinolinone

(VI) (3.9 g), 1-benzylpiperazine (9.6 g) and hexamethylphosphoric triamide (30 ml) was stirred at 120—130 °C for 4 h. After cooling, the mixture was poured into ice-water. The precipitates were collected by filtration, washed with water and dissolved in MeOH containing HCl. The solution was concentrated *in vacuo* and the residue was recrystallized from H_2O–EtOH to give VII (7.0 g, 91%) as colorless needles, mp 293.5—295 °C. IR ν_{max}^{KBr} cm^{-1}: 2820, 1660, 1610, 1509, 1403, 1218. NMR ($CDCl_3$) δ: 2.50—2.83, 3.00—3.30 (each 4H, m, $-N(CH_2CH_2)_2N-$), 3.56 (2H, s, $-CH_2C_6H_5$), 6.06 (1H, s, C_3-aromatic H), 6.77—7.76 (9H, m, aromatic H), 11.08 (1H, br s, $-NHCO-$). *Anal.* Calcd for $C_{20}H_{21}N_3O \cdot HCl$: C, 67.50; H, 6.23; N, 11.81. Found: C, 67.53; H, 6.25; N, 11.84.

4-(1-Piperazinyl)-2(1*H*)-quinolinone Hydrochloride (VIII)——A mixture of VII (7.5 g) and 5% palladium on charcoal (1.0 g) in EtOH–H_2O (300 ml, 3 : 1 mixture) was stirred at 45—50 °C under atmospheric pressure of hydrogen. After the absorption of hydrogen had ceased, the catalyst was filtered off and the filtrate was concentrated *in vacuo*. The residue was recrystallized from EtOH–H_2O to give VIII (5.1 g, 90%) as colorless needles, mp >300 °C. IR ν_{max}^{KBr} cm^{-1}: 3450, 1645, 1609, 1422, 1400, 1328. NMR (DMSO-d_6) δ: 3.26 (8H, br s, $-N(CH_2CH_2)_2N-$), 5.85 (1H, s, C_3- aromatic H), 6.90—7.75 (4H, m, aromatic H), 9.15—10.85 (2H, br, $-NH_2^+-$), 11.35 (1H, br s, $-NHCO-$). *Anal.* Calcd for $C_{13}H_{15}N_3O \cdot HCl \cdot 1/2H_2O$: C, 56.83; H, 6.24; N, 15.30. Found: C, 56.66; H, 6.10; N, 15.54.

2-Acetylamino-β-ethoxyacryloanilide (XI)——A solution of β-ethoxyacryloyl chloride (10.0 g) in absolute DMF (30 ml) was added dropwise to a solution of *o*-acetylaminoaniline (X) (25.0 g) in absolute DMF (100 ml) with stirring and ice-cooling. The mixture was stirred for 1 h at room temperature, then poured into ice-water. The precipitates were collected by filtration and washed with water. Recrystallization from DMF–H_2O gave XI (9.0 g, 78%) as colorless crystals, mp 171—173 °C. IR ν_{max}^{KBr} cm^{-1}: 3320, 1700, 1657, 1618, 1600, 1172. NMR ($CDCl_3$) δ: 1.27 (3H, t, J=6 Hz, $-OCH_2CH_3$), 2.02 (3H, s, $-COCH_3$), 3.91 (2H, q, J=6 Hz, $-OCH_2CH_3$), 6.75 (1H, d, J=12 Hz, $-COCH=$ CH–), 6.90—7.27 (2H, m, aromatic H), 7.35—7.79 [3H, m, 7.51 (1H, d, J=12 Hz, $-COHC=CH-$), aromatic H], 9.13, 9.38 (each 1H, s, $-NHCO-$). *Anal.* Calcd for $C_{13}H_{16}N_2O_3$: C, 62.89; H, 6.50; N, 11.28. Found: C, 62.83; H, 6.52; N, 11.37.

8-Acetylamino-2(1*H*)-quinolinone (XII)——XI (8.5 g) was added slowly to conc. H_2SO_4 (40 ml) with stirring at room temperature. The mixture was stirred for a further 2 h at room temperature, then poured into ice-water. The precipitates were collected by filtration and washed with water. Recrystallization from MeOH–$CHCl_3$ gave XII (5.0 g, 72%) as colorless needles, mp 248—251 °C. IR ν_{max}^{KBr} cm^{-1}: 3291, 1698, 1660, 1612, 1537, 1412. NMR (DMSO-d_6) δ: 2.12 (3H, s, $-COCH_3$), 6.49 (1H, d, J=9 Hz, C_3-aromatic H), 7.10 (1H, dd, $J_1=J_2$=8 Hz, C_6-aromatic H), 7.45, 7.61 (each 1H, dd, J_1=8 Hz, J_2=2 Hz, C_5-, C_7-aromatic H), 7.88 (1H, d, J=9 Hz, C_4-aromatic H), 9.47, 10.97 (each 1H, br s, $-NHCO-$). *Anal.* Calcd for $C_{11}H_{10}N_2O_2$: C, 65.34; H, 4.98; N, 13.85. Found: C, 65.14; H, 5.05; N, 14.02.

8-Acetylamino-3,4-dihydro-2(1*H*)-quinolinone (XIII)——A mixture of XII (15.0 g) and 10% palladium on charcoal (1.5 g) in dioxane (300 ml) was stirred at 70—80 °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 to give XIII (14.3 g, 94%) as colorless needles, mp 196—197 °C. IR ν_{max}^{KBr} cm^{-1}: 3340, 3225, 1700, 1663, 1537, 1395. NMR (DMSO-d_6) δ: 2.05 (3H, s, $-COCH_3$) 2.15—3.13 (4H, m, $-CH_2CH_2-$), 6.60—7.45 (3H, m, aromatic H), 9.27 (2H, br s, 2×$-NHCO-$). *Anal.* Calcd for $C_{11}H_{12}N_2O_2$: C, 64.69; H, 5.92; N, 13.72. Found: C, 64.63; H, 5.87; N, 13.53.

Preparation of 8-Amino-2(1*H*)-quinolinone Derivatives (XIVb, XVd). 8-Amino-2(1*H*)-quinolinone (XIVb)——A mixture of XII (21.5 g) and 20% HCl (190 ml) was heated under reflux for 1 h. After cooling, the mixture was poured into ice-water, then neutralized with 5 N NaOH. The precipitates were collected by filtration and washed with water. Recrystallization from DMF gave XIVb (14.8 g, 87%) as yellow needles, mp 252—254 °C (dec.). IR ν_{max}^{KBr} cm^{-1}: 3470, 3030, 1681, 1642, 1611, 1452, 1322, NMR (DMSO-d_6) δ: 5.49 (2H, s, $-NH_2$), 6.43 (1H, d, J=9 Hz, C_3-aromatic H), 6.63—7.10 (3H, m, aromatic H), 7.75 (1H, d, J=9 Hz, C_4-aromatic H), 10.83 (1H, br s, $-NHCO-$). *Anal.* Calcd for $C_9H_8N_2O$: C, 67.49; H, 5.03; N, 17.49. Found: C, 67.55; H, 5.08; N, 17.59.

The free base of XVd (84%) was obtained in the same manner as described for XIVb. XVd was recrystallized from EtOH to give colorless needles, mp 224—225 °C. IR ν_{max}^{KBr} cm^{-1}: 3450, 3370, 3260, 1681, 1645, 1601, 1500, 1400. NMR (DMSO-d_6) δ: 2.20—2.97 (4H, m, $-CH_2CH_2-$), 4.98—6.65 (2H, br, $-NH_2$), 6.70—6.98 (3H, m, aromatic H), 9.60 (1H, br s, $-NHCO-$). *Anal.* Calcd for $C_9H_{10}N_2O \cdot HCl$: C, 54.41; H, 5.58; N, 14.10. Found: C, 54.64; H, 5.53; N, 14.55.

Preparation of (1-Piperazinyl)-2(1*H*)-quinolinone Derivatives (XVIa—d, XVIIIa, b, XXV). 3,4-Dihydro-6-(1-piperazinyl)-2(1*H*)-quinolinone Hydrobromide (XVIb)——A mixture of 6-amino-3,4-dihydro-2(1*H*)-quinolinone (XVb) (21.1 g, 0.13 mol) and bis(β-bromoethyl)amine hydrobromide (40.5 g, 0.13 mol) in EtOH (150 ml) was heated under reflux with stirring for 8 h, then cooled. Na_2CO_3 (13.8 g, 0.13 mol) was added to the mixture, then the whole was heated under reflux with stirring for 8 h. The mixture was cooled to room temperature. The precipitates were collected by filtration and washed with EtOH. Recrystallization from EtOH–H_2O gave XVIb (26.0 g, 64%) as colorless needles, mp 289—293 °C (dec.). IR ν_{max}^{KBr} cm^{-1}: 3230, 3075, 1695, 1685, 1602, 1517, 1390, 1249. NMR (DMSO-d_6) δ: 2.23—3.10 (4H, m, $-CH_2CH_2-$), 3.26 (8H, s, $-N(CH_2CH_2)_2N-$), 3.40—5.50 (2H, br, $-NH_2^+-$), 6.60—7.00 (3H, m, aromatic H), 9.88 (1H, s, $-NHCO-$). The elemental analysis data are given in Table II.

Compounds XVIa, c, d, XVIIIa, b and XXV were obtained in the same manner as described for XVIb. Compound XVIa was obtained by treatment of the free base of XVIa with HCl in MeOH in the usual manner. The

yield, melting point and elemental analysis data are given in Table II.

Preparation of 1-Alkyl-3,4-dihydro-6-[4-(3,4-dimethoxybenzoyl)-1-piperazinyl]-2(1*H*)-quinolinone Derivatives (XXa, b). 3,4-Dihydro-6-[4-(3,4-dimethoxybenzoyl)-1-piperazinyl]-1-propargyl-2(1*H*)-quinolinone (XXa)——A solution of XVIIb-1 (0.5 g) in absolute DMF (7 ml) was treated with 50% NaH (0.07 g, dispersion in oil) with stirring under a nitrogen atmosphere. The mixture was stirred at room temperature for 1 h, then a solution of propargyl bromide (0.23 g) in absolute DMF (3 ml) was added dropwise and the mixture was stirred at room temperature for 1 h. The mixture was poured into ice-water and extracted with $CHCl_3$. The $CHCl_3$ solution was washed with water, dried (Na_2SO_4) and concentrated *in vacuo*. The residue was recrystallized from EtOH to give XXa (0.18 g, 32%) as yellow crystals, mp 152—154 °C. IR ν_{max}^{KBr} cm^{-1}: 3160, 2100, 1663, 1428, 1019. NMR ($CDCl_3$) δ: 2.20 (1H, t, J=2 Hz, $-C\equiv C\underline{H}$), 2.27—3.01 (4H, m, $-C\underline{H}_2C\underline{H}_2-$), 3.01—3.33 (4H, m, $-N(C\underline{H}_2CH_2)_2NCO-$), 3.60—4.03 [10H, m, $-CON(C\underline{H}_2CH_2)_2N-$, 3.89 (6H, s, 2×$-OC\underline{H}_3$)], 4.65 (2H, d, J=2 Hz, $-C\underline{H}_2C\equiv CH$), 6.67—7.33 (6H, m, aromatic H). The elemental analysis data are given in Table III.

Compound XXb was obtained in the same manner as described for XXa and the yield, melting point and elemental analysis data are given in Table III.

8-Acetoxy-3,4-dihydro-6-nitro-2(1*H*)-quinolinone (XXII)——A mixture of 3,4-dihydro-8-hydroxy-2(1*H*)-quinolinone (XXI) (12.0 g) and conc. H_2SO_4 (0.05 ml) in Ac_2O (100 ml) was stirred at 75—80 °C for 1.5 h, then cooled at 0—5 °C in an ice-water bath. AcOH (20 ml) was added to the mixture. A solution of fuming HNO_3 (3.4 ml) in AcOH (10 ml) was then added dropwise with stirring and ice-cooling. The whole was stirred at room temperature for 2 h, then poured into ice-water. The precipitates were collected by filtration and washed with water. Recrystallization from DMF gave XXII (15.6 g, 85%) as pale yellow crystals, mp 284—286 °C (dec.). IR ν_{max}^{KBr} cm^{-1}: 3115, 1784, 1691, 1601, 1525, 1500, 1344, 1327. NMR (DMSO-d_6) δ: 2.31 (3H, s, $-COC\underline{H}_3$), 2.38—3.20 (4H, m, $-C\underline{H}_2C\underline{H}_2-$), 7.96, 8.02 (each 1H, d, J=2 Hz, C_5-, C_7-aromatic H), 11.55 (1H, br s, $N\underline{H}CO-$). *Anal.* Calcd for $C_{11}H_{10}N_2O_5$: C, 52.80; H, 4.03; N, 11.20. Found: C, 52.76; H, 4.09; N, 11.28.

3,4-Dihydro-8-methoxy-6-nitro-2(1*H*)-quinolinone (XXIII)——A mixture of XXII (6.0 g), K_2CO_3 (7.3 g) and MeI (10.0 g) in DMF (70 ml)–H_2O (20 ml) was stirred at 40—50 °C for 2 h. After cooling, the mixture was poured into ice-water. The precipitates were collected by filtration and washed with water. Recrystallization from EtOH–$CHCl_3$ gave XXIII (4.0 g, 75%) as yellow needles, mp 225—226 °C. IR ν_{max}^{KBr} cm^{-1}: 3225, 1685, 1522, 1503, 1326, 1305, 1286. NMR (DMSO-d_6) δ: 2.32—3.12 (4H, m, $-C\underline{H}_2C\underline{H}_2-$), 3.85 (3H, s, $-OC\underline{H}_3$), 7.63, 7.77 (each 1H, d, J=2 Hz, C_5-, C_7-aromatic H), 9.58 (1H, br s, $-N\underline{H}CO-$). *Anal.* Calcd for $C_{10}H_{10}N_2O_4$: C, 54.05; H, 4.54; N, 12.61. Found: C, 54.10; H, 4.51; N, 12.61.

6-Amino-3,4-dihydro-8-methoxy-2(1*H*)-quinolinone (XXIV)——A mixture of XXIII (3.5 g) and 5% palladium on charcoal (0.4 g) in DMF (50 ml) was stirred at room temperature 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 to give XXIV (2.6 g, 86%) as colorless needles, mp 153—154 °C IR ν_{max}^{KBr} cm^{-1}: 3470, 3425, 3210, 1675, 1610, 1515, 1110. NMR ($CDCl_3$) δ: 2.32—2.93 (4H, m, $-C\underline{H}_2C\underline{H}_2-$) 3.22 (2H, br s, $-N\underline{H}_2$), 3.72 (3H, s, $-OC\underline{H}_3$), 6.07, 6.12 (each 1H, d, J=2 Hz, C_5-, C_7-aromatic H), 7.61 (1H, br s, $-N\underline{H}CO-$). *Anal.* Calcd for $C_{10}H_{12}N_2O_2$: C, 62.48; H, 6.29; N, 14.58. Found: C, 62.28; H, 6.17; N, 14.64.

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 preparations were prepared according to the methods of Endoh and Hashimoto (1970)[17] and Kubota and Hashimoto (1973),[18] respectively. The preparations were cross-circulated through the cannulated arteries with blood from a donor dog anesthetized with sodium pentobarbital and receiving heparin. Perfusion pressure was kept constant at 100 mmHg. The papillary muscle was stimulated at a frequency of 2 Hz and tension developed by the papillary muscle was measured with a force displacement transducer. Sinus rate was measured by the use of a cardiotachometer triggered by developed tension of the right atrium. Blood flow through the cannulated arteries was measured with an electromagnetic flowmeter. Recording of these parameters was done on an ink-writing rectigraph. The compounds were injected intra-arterially with microsyringes.

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