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A Synthesis of 3-Amino-4-hydroxyquinolin-2(1H)-one Derivatives *via* Oxazolo[4,5-*c*]quinolin-4(5H)-ones[1)]

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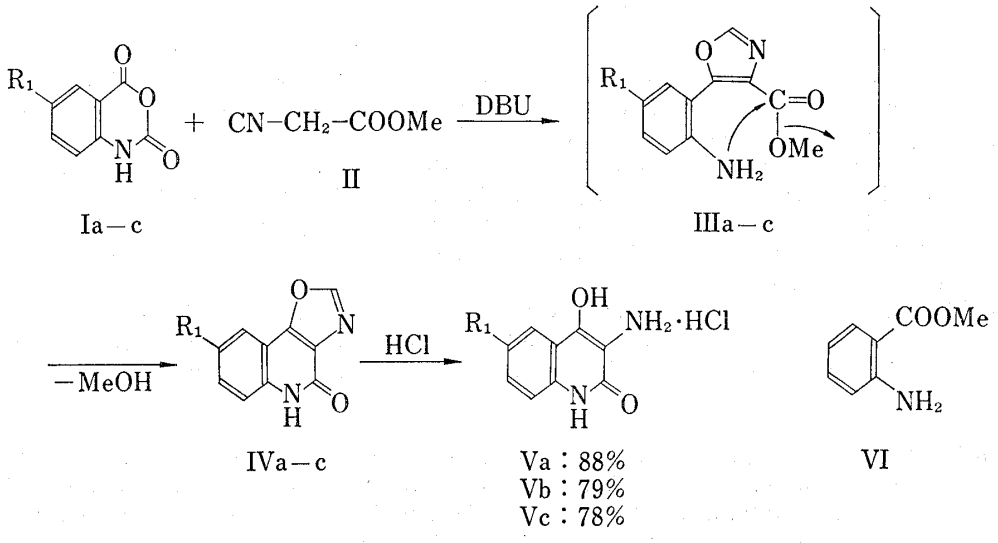
3-Amino-4-hydroxyquinolin-2(1H)-one compounds (aminocarbostyrils) were synthesized by a reaction of methyl isocyanoacetate with isatoic anhydrides in the presence of 1,8-diazabicyclo[5,4,0]undec-7-ene (DBU), followed by hydrolysis with HCl. The alkylation of oxazolo[4,5-*c*]quinolin-4(5H)-ones which are the intermediates of the aminocarbostyrils and the acylation of aminocarbostyrils were also investigated. Furthermore, a variety of the quinolin-2(1H)-one analogs showed antiallergic activity.

Keywords——aminohydroxyquinolin-2(1H)-one; aminocarbostyril; oxazolocarbostyril; isocyanoacetate; isatoic anhydride; antiallergic activity; passive cutaneous anaphylaxis reaction

Quinolin-2(1H)-ones (carbostyrils) are analog of quinoline compounds and have various interesting biological activities. For example, Buckle, *et al.*[3)] have recently reported that 3-nitro-4-hydroxyquinolin-2(1H)-one analogs possess antiallergic activity as measured by the homocytotropic antibody-antigen induced passive cutaneous anaphylaxis (PCA) reaction in rats. Thus, the synthesis of 3-amino-4-hydroxyquinolin-2(1H)-one (aminocarbostyril) derivatives having the amino group instead of the nitro group would be of interest in both chemical and pharmacological points of view.



a : R_1=H, b : R_1=OMe, c : R_1=Me

Chart 1

1) This paper constitutes Part 2 of the series entitled "Synthesis of Heterocyclic Compounds using Isocyano Compounds." Part 1: M. Suzuki and N. Yoneda, *J. Org. Chem.*, **41**, 1482 (1976). This study was presented at the 26th Annual Meeting of the Kinki Branch of the Pharmaceutical Society of Japan, Osaka, October 1976.

2) Location: *16–89Kashima-3-chome, Yodogawa-ku, Osaka.*

3) D.R. Buckle, B.C.C. Cantello, H. Smith, and B.A. Spicer, *J. Med. Chem.*, **18**, 726 (1975).

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As regards the synthesis of the aminocarbostyril compounds, we have reported the reaction of methyl isocyanoacetate (II) with 4H-3,1-benzoxazin-4-one compounds, followed by hydrolysis to afford the aminocarbostyril analogs in the preceding paper.[4] Now, we wish to report a convenient synthesis of the aminocarbostyrils (V) by a reaction of II with 2H-3,1-benzoxazine 2,4(1H)-diones (isatoic anhydrides) (I).

The reaction of isatoic anhydride (Ia) with an equimolar II[5] was carried out in the presence of 1,8-diazabicyclo[5,4,0]undec-7-ene (DBU), a very strong organic base, as a base in tetrahydrofuran as shown in Chart 1.

As a result, oxazolo[4,5-*c*]quinolin-4(5H)-one (IVa) was isolated from the reaction mixture in 45% yield, methyl anthranilate (VI) being also afforded in nearly same yield as a by-product.

It is assumed that the oxazoloquinoline derivative (IVa) was formed through the intramolecular amidation of the decarboxylated oxazole (IIIa) and the by-product (VI) would be formed by the attack of the methoxy anion separated from methoxycarbonyl group in IIIa to benzoxazine compound (Ia). Therefore, the use of two equimolar Ia and DBU increased the yield of the product (IVa) up to 90%. Similarly, the reaction using various isatoic anhydrides (Ib, Ic) was carried out and the results are summarized in Table I.

Table I. Oxazolo[4,5-*c*]quinoline-2(1H)-ones (IVa—c and VIIIa—e)

Compd.	Yield (%)	mp (°C) Recryst. (solvent)	IR ν_{max}^{Nujol} cm^{-1}	NMR δ CH[a] (solvent)	Formula	Analysis (%) Calcd. (Found) C	H	N
IVa	90	>270 (DMSO)	3110, 1680, 1630, 1570	8.86 (CF_3COOD)	$C_{10}H_6N_2O_2$	64.51 (64.16)	3.24 (3.53)	15.04 (14.92)
IVb	79	>270 (DMSO)	3150, 1670, 1633, 1580	8.81 (CF_3COOD)	$C_{11}H_8N_2O_3$	61.11 (60.82)	3.73 (3.90)	12.96 (12.74)
IVc	75	>270 (DMSO)	3100, 1675, 1640, 1595	8.82 (CF_3COOD)	$C_{11}H_8N_2O_2$	65.99 (66.17)	4.03 (4.20)	13.99 (13.96)
VIIIa	85	189—192[b] (MeOH)	3100, 1670, 1640, 1585	8.80 (DMSO-d_6)	$C_{11}H_8N_2O_2$	65.99 (65.82)	4.03 (4.33)	13.99 (13.86)
VIIIb	78	160—161 (AcOEt)	3130, 1670, 1640, 1590	8.91 (DMSO-d_6)	$C_{12}H_{10}N_2O_2$	67.27 (67.23)	4.70 (4.86)	13.07 (12.90)
VIIIc	83	210—211 (MeOH)	3140, 1720, 1690, 1645, 1590	8.85 (DMSO-d_6)	$C_{13}H_{10}N_2O_3$	64.45 (64.23)	4.16 (4.42)	11.56 (11.46)
VIIId	80	128—129 (EtOH)	3100, 1680, 1640, 1590	8.83 (DMSO-d_6)	$C_{13}H_{10}N_2O_2$	69.01 (68.87)	4.45 (4.57)	12.38 (12.38)
VIIIe	80	248—250 (DMSO)	3250, 3100, 2130, 1665, 1640, 1590	8.85 (CF_3COOD)	$C_{13}H_8N_2O_2$	69.63 (69.25)	3.59 (3.86)	12.49 (12.40)

a) Methin proton of the oxazole ring. b) Lit.,[5] 191—194°.

The oxazolo[4,5-*c*]quinolin-4(5H)-ones (IVa—c) thus obtained were hydrolyzed with methanolic hydrochloric acid at 50—55° for 1 hr to afford 3-amino-4-hydroxyquinolin-2(1H)-one derivatives (Va—c) in good yields. The resulting products (Va—c) were identical with the compounds (V) derived by the reaction of 4H-3,1-benzoxazin-4-one with methyl isocyanoacetate in the physicochemical properties.[4]

Furthermore, these results were applied to the preparation of 1-substituted aminocarbostyrils. Namely the reaction of a variety of N-substituted isatoic anhydrides (VIIa—e), which were easily prepared by the alkylation of isatoic anhydride,[6] with methyl isocyano-

4) K. Matsumoto, M. Suzuki, N. Yoneda, and M. Miyoshi, *Synthesis* **1976**, 805.
5) A similar reaction in the presence of sodium hydride has been independently reported by G.M. Coppola, G.E. Hardtmann, and O.R. Pfister, *J. Org. Chem.*, **41**, 825 (1976).
6) G.E. Hardtmann, G. Koletar, and O.R. Pfister, *J. Heterocycl. Chem.*, **12**, 565 (1975).

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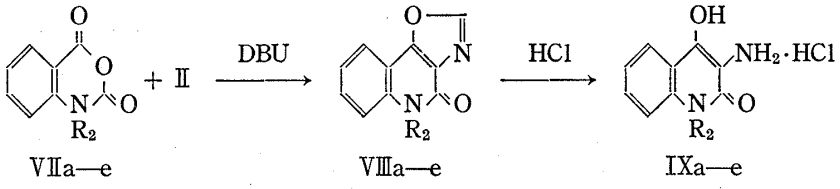
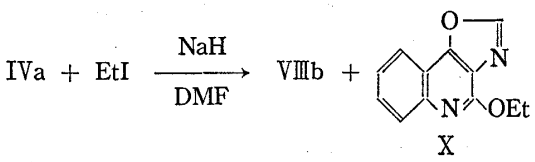
acetate (II) was carried out in a similar manner. Consequently, the expected N-substituted oxazolo-[4,5-*c*]quinolin-4(5H)-ones (VIIIa—e) were obtained in good yields as listed in Table I.

Subsequently, VIIIa—e thus obtained were hydrolyzed with hydrochloric acid at 50° to afford 1-substituted 3-amino-4-hydroxyquinolin-2(1H)-one hydrochlorides (IXa—e). The structure of the resulting products (IXa—e) was confirmed by the various physicochemical data and the elemental analyses as summarized in Table II.



VIIa—e VIIIa—e IXa—e

a: R_2=Me, b: R_2=Et, c: R_2=CH_2COCH_3, d: R_2=$CH_2CH{=}CH_2$, e: R=$CH_2C{\equiv}CH$



X

Chart 2

Table II. 1-Substituted 3-Amino-4-hydroxyquinolin-2(1H)-one Hydrochloride (IXa—e)

IX	Yield (%)	mp (°C) (dec.)	IR ν_{max}^{Nujol} (cm^{-1})	NMR δ (DMSO-d_6)	Formula	Analysis (%) Calcd. (Found) C	H	N	Mass (M^+-HCl)
a	89	>260	1650, 1620, 1600	8.90 (b, 4H), 7.10—8.20 (m, 4H), 3.67 (s, 3H)	$C_{10}H_{11}ClN_2O_2$	52.98 (52.88)	4.44 (4.63)	12.35 (12.78)	190
b	82	235—239	1640, 1620, 1595	8.40 (b, 4H), 7.20—8.40 (m,4H), 4.38 (q, J=7 Hz, 2H), 1.24 (t, J=7 Hz, 3H)	$C_{11}H_{13}ClN_2O_2$	54.89 (54.46)	5.44 (5.57)	11.64 (11.57)	204
c	88	233—236	1728, 1650, 1615, 1600	7.00—8.30 (m, 8H), 5.30 (s, 2H), 2.32 (s, 3H)	$C_{12}H_{13}ClN_2O_3$	53.64 (53.47)	4.88 (4.92)	10.43 (10.72)	232
d	72	213—215	1640, 1615, 1600	9.55 (b, 4H), 7.80—8.50 (M, 4H), 5.70—6.30 (m, 1H), 4.80—5.30 (m, 4H)	$C_{12}H_{13}ClN_2O_2$	57.03 (56.87)	5.18 (5.23)	11.08 (11.15)	216
e	90	200—202	1650, 1620, 1595	6.40—8.40 (m, 8H), 5.13 (d, J=3 Hz 2H), 3.30 (t, J=3 Hz, 1H)	$C_{12}H_{11}ClN_2O_2$	57.49 (57.67)	4.42 (4.51)	11.18 (11.48)	214

On the other hand, the alkylation of oxazolo[4,5-*c*]quinolin-4(5H)-one (IVa) was also investigated. The reaction of IVa with ethyl iodide was carried out in the presence of sodium hydride (NaH) in dimethylformamide (DMF) at room temperature and two products were observed on thin-layer chromatography (TLC). As described in the experimental section, the separation using silica gel column chromatography gave two crystalline products having mp 160—161° and mp 109—110° in 62% and 7% yields, respectively. The former compound having a higher melting point agreed with 5-ethyloxazolo[4,5-*c*]quinolin-4(5H)-one (VIIIb) in all spectral data. On the other hand, the infrared (IR) spectrum of the latter showed the characteristic absorption based on the methine group of the oxazole ring at 3100 cm^{-1} but no absorption of the CO streching vibration based on the amide group at near 1670 cm^{-1}. The nuclear magnetic resonance (NMR) spectrum showed the presence of a singlet peak of methine proton at 9.02 ppm, aromatic protons at 7.50—8.30 ppm (m, 4H), O-methylene

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proton at 4.69 ppm (q, J=7 Hz, 2H), and C-methyl proton at 1.50 ppm (t, J=7 Hz, 3H). Furthermore, from the mass spectrum m/e, 214 (M^+) and the elemental analyses, the structure of the product was identified as 4-ethoxyoxazolo[4,5-*c*]quinoline (X) which would be formed by the O-alkylation of IVa. From these results, it was found that the use of N-alkylated isatoic anhydride was more advantageous for the preparation of N-alkylated aminocarbostyrils without formation of the O-alkylated product.

The acylation of the 3-amino group of aminocarbostyril compounds (Va and IXa) was also carried out using acetic anhydride or benzoyl chloride in pyridine or dilute alkaline solution as shown in Chart 3, and the corresponding 3-acylamino-4-hydroxyquinolin-2(1H)-ones (XIa—c) were obtained in good yields. In this reaction, only the acylation to the NH_2 group proceeded without accompanying acylation of the OH group.

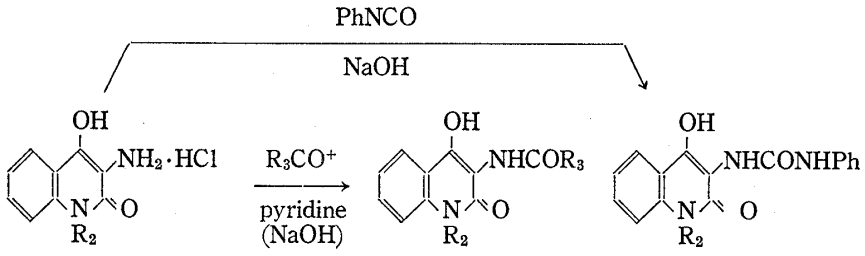

Chart 3

Furthermore, the preparation of ureido compounds using isocyanates was investigated; for example, the reaction of IXa with phenylisocyanate in dilute alkaline solution gave 1-methyl-3-N′-phenylureido-4-hydroxyquinolin-2(1H)-one (XII) in 65% yield.

The pharmacological assay for antiallergic activity of various quinolin-2(1H)-one analogs obtained here was carried out, and consequently considerable number of the compounds inhibited homologous PCA reaction in the rat induced by reaginic antibody[7] as shown in Table III.

Table III. PCA Reaction

Compound	IVa	IVb	IVc	Va	Vb	Vc	IXa	IXb	IXc	IXd	XIa	XIc	XII	Disodium Chromoglicate
Inhibition (%)	44	42	12	34	9	0	44	51	44	47	20	51	37	75—80

Experimental

Melting points are uncorrected and were measured by the use of a Yamato melting point apparatus. IR spectra were recorded on a Shimadzu IR-27G infrared spectrophotometer. NMR spectra were obtained using a Hitachi Perkin-Elmer R-20A High Resolution NMR spectrometer with tetramethylsilane as internal standard. MS were recorded on a Hitachi RMU-6M spectrometer.

Typical Preparation of Oxazolo[4,5-*c*]quinolin-4(5H)-ones (IVa—c)——Isatoic anhydride (Ia, 3.90 g, 0.02 mol) was added portionwise to a stirred mixture of methyl isocyanoacetate (II, 0.97 g, 0.01 mol), DBU (3.04 g, 0.02 mol) and tetrahydrofuran (THF) (30 ml) at 23—25°. Stirring was continued for 48 hr at room temperature and precipitates appeared during this time. The mixture was neutralized with 10% AcOH under cooling and H_2O (20 ml) was added to the mixture. The precipitates were isolated by filtration and

7) O.T.S.C. Orr, M.C. Pollard, J.G. William, and J.S.G. Cox, *Clin. Exp. Immunol.*, **7**, 745 (1970).

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washed with H_2O and MeOH. Recrystallization from DMSO afforded oxazolo[4,5-*c*]quinolin-4(5H)-one (IVa, 2.50 g, 90%) as colorless prisms: mp>270°. IR ν_{max}^{Nujol} cm^{-1}: 3110, 1680, 1630. NMR (in CF_3COOD) δ: 8.86 (1H, s, CH), 7.50—8.50 (4H, m, aromatic proton). MS *m/e*: 186 (M^+).

On the other hand, the above filtrate was concentrated to remove the solvent under reduced pressure and the resulting residue was extracted with AcOEt. The extract was washed with H_2O, dried over Na_2SO_4, and evaporated *in vacuo*. The residual oil was distilled under reduced pressure to give methyl anthranilate (VI, 1.28 g, 85%): bp 131—132° (12 mmHg). The compound was spectroscopically concordant with an authentic specimen.[8]

In a similar way, 8-methoxyoxazolo[4,5-*c*]quinolin-4(5H)-one (IVb) and 8-methyloxazolo[4,5-*c*]quinolin-4(5H)-one (IVc) were prepared using 6-methoxyisatoic anhydride (Ib) and 6-methylisatoic anhydride (Ic), respectively, and these results are summarized in Table I.

General Synthesis of N-Substituted Oxazolo[4,5-*c*]quinolin-4(5H)-ones (VIIIa—e)——N-Alkylated isatoic anhydride (VIIa—e, 0.02 mol), which was easily prepared by the reaction of isatoic anhydride with alkyl halide in the presence of NaH in DMF,[6] was added portionwise to a stirred mixture of methyl isocyanoacetate (II, 0.97 g, 0.01 mol), DBU (3.04 g, 0.02 mol) and THF (30 ml) at 30°. After stirring was continued for 3—5 hr at room temperature, the same treatment described above was carried out. Recrystallization from suitable solvent afforded the corresponding N-substituted oxazolo[4,5-*c*]quinolin-4(5H)-one (VIIIa—e). These results are summarized in Table I.

General Synthesis of 3-Amino-4-hydroxyquinolin-2(1H)-one Derivatives (Va—c) and IXa—e)——The oxazolo[4,5-*c*]quinoline compound (IVa—c and VIIIa—e, 1.0 g) was dissolved in a mixture of concentrated HCl (5 ml) and MeOH (25 ml) at 50—55° with stirring. Stirring was continued for 1 hr at the same temperature, and then resulting precipitates were isolated by suction under cooling and washed with a small amount of cold MeOH and $(C_2H_5)_2O$ to afford analytically pure 3-amino-4-hydroxyquinolin-2(1H)-one hydrochlorides (Va—c and IXa—e). Of these, the physicochemical properties of the product (Va—c) were homogeneous with those of the compound obtained by the method described in the previous paper.[4] Moreover, 1-methyl-3-amino-4-hydroxyquinolin-2(1H)-one hydrochloride (IXa) was spectroscopically identical with an authentic specimen.[9] Another products (IXb—e) were confirmed by the spectral data and the elemental analyses as shown in Table II.

Reaction of IVa with Ethyl Iodide——To a suspension of NaH (65% in oil, 962 mg, 0.026 mol) in DMF (50 ml) was added portionwise IVa (3.72 g, 0.02 mol) over a period of 15 min at 25—30° with stirring. After the mixture was stirred for 1 hr, ethyl iodide (3.43 g, 0.022 mol) was added dropwise to the mixture at 35° and then stirring was continued for 18 hr at room temperature. After the reaction was over, the solvent was removed *in vacuo* and the resulting residue was extracted with AcOEt. The extract was washed with saturated NaCl solution, dried over Na_2SO_4 and then evaporated under reduced pressure. Column chromatography of the resulting residue over silica gel (130 g, Kieselgel 60, 0.063—0.2 mm, Merck) using $CHCl_3$ as eluent gave 4-ethoxyoxazolo[4,5-*c*]quinolin (X, 350 mg, 7%) from the first fraction. Recrystallization from EtOH afforded analytically pure compound (X) as colorless needles: mp 109—110°. IR ν_{max}^{Nujol} cm^{-1}; 3100, 1640, 1600, 1570. NMR (in DMSO-d_6) δ: 9.02 (1H, s, CH), 7.50—8.30 (4H, m, aromatic proton), 4.69 (2H, q, J=7 Hz, CH_2), 1.50 (3H, t, J=7 Hz, CH_3). *Anal.* Calcd. for $C_{12}H_{10}N_2O_2$: C, 67.27; H, 4.70; N, 13.07. Found: C, 67.05; H, 4.85; N, 12.96.

From the second fraction, 5-ethyloxazolo[4,5-*c*]quinolin-4(5H)-one (VIIIb, 2.66 g, 62%) was obtained. Recrystallization from AcOEt gave colorless needles: mp 160—161°. IR ν_{max}^{Nujol} cm^{-1}: 3130, 1670, 1640, 1590. NMR (in DMSO-d_6) δ: 8.91 (1H, s, CH). 7.30—8.10 (4H, m, aromatic proton), 4.42 (2H, q, J=7 Hz, CH_2), 1.30 (3H, t, J=7 Hz, CH_3). This compound agreed with VIIIb obtained by the reaction of methyl isocyanoacetate (II) with N-ethylisatoic anhydride (VIIb) in the IR and NMR spectral data.

3-Acetylamino-4-hydroxyquinolin-2(1H)-one (XIa)——To a solution of Va (2.13 g, 0.01 mol) dissolved in pyridine (20 ml) was added dropwise acetic anhydride (1.22 g, 0.012 mol) at 25—28° with stirring. After stirring was continued for 18 hr at room temperature, H_2O (20 ml) was added to the mixture and the resulting precipitates were filtered by suction and washed with H_2O. Recrystallization from MeOH afforded XIa (1.8 g, 83%) as colorless needles: mp 246—248°. IR ν_{max}^{Nujol} cm^{-1}: 3200, 1670, 1620, 1610. NMR (in DMSO-d_6) δ: 12.10 (1H, broad, NHCO–), 11.85 (1H, broad, OH), 9.72 (1H, s, NHCOCH$_3$), 7.00—8.00 (4H, m, aromatic proton), 2.29 (3H, s, CH_3). *Anal.* Calcd. for $C_{11}H_{10}N_2O_3$: C, 60.55; H, 4.62; N, 12.84. Found: C, 60.62; H, 4.62; N, 12.37.

1-Methyl-3-acetylamino-4-hydroxyquinolin-2(1H)-one (XIb)——To a solution of IXa (2.26 g, 0.01 mol) dissolved in 5% NaOH (20 ml) was added dropwise acetic anhydride (1.03 g, 0.01 mol) at 10—15° with stirring. After stirring was continued for 2 hr at the same temperature, H_2O (20 ml) was added to the mixture and then the mixture was adjusted to pH 1 with 10% HCl under cooling. The resulting precipitates were filtered by suction and washed with H_2O. Recrystallization from AcOEt afforded XIb (2.0 g, 87%) as colorless needles: mp 187—189°. IR ν_{max}^{Nujol} cm^{-1}: 3250, 1635, 1610, 1585. NMR (in DMSO-d_6) δ: 12.07 (1H, s, OH), 9.72

8) Available from Tokyo Kasei Kogyo Co., Ltd., Tokyo, Japan.
9) H. Waldmann, *J. Prakt. Chem.*, **147**, 321 (1937) [*Chem. Abstr.*, **31**, 1813 (1937)].

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(1H, s, NH), 7.20—8.20 (4H, m, aromatic proton), 3.69 (3H, s, N-CH_3), 2.31 (3H, s, $COCH_3$). *Anal.* Calcd. for $C_{12}H_{12}N_2O_3$: C, 62.06; H, 5.20; N, 12.06. Found: C, 61.82; H, 5.28; N, 11.92.

1-Methyl-3-benzoylamino-4-hydroxyquinolin-2(1H)-one (XIc)——To a solution of IXa (1.13 g, 0.005 mol) dissolved in 5% NaOH (10 ml) was added dropwise benzoyl chloride (1.15 g, 0.011 mol) at 10—12° with stirring. After stirring was continued for 2 hr at room temperature, the same treatment was carried out according to the procedure for XIa and recrystallization from DMF–MeOH afforded XIc (0.9 g, 61%) as colorless prisms: mp 185—186°. IR ν_{max}^{Nujol} cm^{-1}: 3300, 1645, 1615, 1590. NMR (in DMSO-d_6) δ: 11.72 (1H, s, OH), 9.70 (1H, broad, NH), 7.20—8.20 (9H, m, aromatic proton) 3.67 (3H, s, CH_3). *Anal.* Calcd. for $C_{17}H_{14}N_2O_3$: C, 69.37; H, 4.79; N, 9.51. Found: C, 68.93; H, 4.94; N, 9.51.

1-Methyl-3-N′-phenylureido-4-hydroxyquinolin-2(1H)-one (XII)——To a solution of IXa (1.13 g, 0.005 mol) dissolved in 5% NaOH (7 ml) and EtOH (5 ml) was added dropwise phenylisocyanate (0.6 g, 0.005 mol) at 25—28° with stirring. After stirring was continued for 2 hr at room temperature, H_2O (20 ml) was added to the mixture and precipitates were filtered by suction. Subsequently the precipitates were dissolved in MeOH and the solution was adjusted to pH 1 with 10% HCl. The resulting crystals were collected by filtration and recrystallized from AcOEt to afford XII (1.0 g, 65%) as colorless needles: mp 199—201°. IR ν_{max}^{Nujol} cm^{-1}: 3300, 3150, 3100, 1635, 1607, 1597. NMR (in DMSO-d_6) δ: 12.90 (1H, s, OH), 10.11 (1H, broad s, NH), 8.78 (1H, broad s, NH), 7.00—8.20 (9H, m, aromatic proton), 3.70 (3H, s, CH_3). *Anal.* Calcd. for $C_{17}H_{15}N_3O_3$: C, 66.00; H, 4.88; N, 13.58. Found: C, 65.62; H, 4.95; N, 13.56.

Antiallergic Activity——PCA test was carried out according to the method described by Orr, *et al.*[7] using Male Wistar rats weighing about 200—250 g. These results are summarized in Table III.

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