[Chem. Pharm. Bull. 32(6)2160—2164(1984)]

Studies on 4(1*H*)-Quinazolinones. IV.[1a] Convenient Syntheses of 12-Methyl-6*H*-isoquino[2,1-*a*]quinazolin-6-one and 6-Methyl-13*H*-quinazolino[3,4-*a*]quinazolin-13-one

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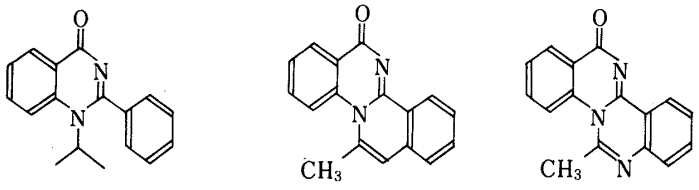
(Received September 22, 1983)

Two novel ring systems, 12-methyl-6*H*-isoquino[2,1-*a*]quinazolin-6-one (**2**) and 6-methyl-13*H*-quinazolino[3,4-*a*]quinazolin-13-one (**3a**), were synthesized. Reaction of 3-methylisocoumarin (**4**) with 2-cyanoaniline gave 2-(2-cyanophenyl)-3-methylisocarbostyril (**5**), which was converted to 2-(2-carbamoylphenyl)-3-methylisocarbostyril (**6**) by treatment with alkaline hydrogen peroxide. The cyclization of **6** with boron trifluoride etherate afforded **2**. Compound **3a** was prepared by the reaction of 2-methyl-4*H*-3,1-benzoxazin-4-one (**8a**) with 2-cyanoaniline in one step. Some derivatives (**3b**—**g**) were also prepared by this method. The reaction mechanism is discussed.

Keywords——4(1*H*)-quinazolinone; isoquino[2,1-*a*]quinazolinone; quinazolino[3,4-*a*]-quinazolinone; 4*H*-3,1-benzoxazin-4-one; amidine intermediate; antiinflammatory activity

Our studies on 4(1*H*)-quinazolinones[1a] have shown that 1-isopropyl-2-phenyl-4(1*H*)-quinazolinone (**1**)[1b] and its derivatives have potent antiinflammatory activity. In connection with their structure–activity relationship, we were interested in the conformational requirements for the activity. Therefore, our efforts were directed toward the synthesis of fused quinazolinones, 12-methyl-6*H*-isoquino[2,1-*a*]quinazolin-6-one (**2**) and 6-methyl-13*H*-quinazolino[3,4-*a*]quinazolin-13-one (**3a**), in which the aromatic rings are coplanar to one another. This report presents convenient syntheses of these novel ring systems.



1 2 3a

Chart 1

The method for the synthesis of **2** is shown in Chart 2. 3-Methylisocoumarin (**4**) was prepared from (2-carboxyphenyl)acetone[2] by a slight modification of Beugelmans' method.[3] Treatment of **4** with 2-cyanoaniline in the presence of potassium *tert*-butoxide in tetrahydrofuran (THF) gave the isocarbostyril **5**. Direct ring closure of **5** to **2** by treatment with methanolic hydrogen chloride[4] was attempted, but 2-(2-methoxycarbonylphenyl)-3-methylisocarbostyril (**7**) was obtained. Therefore, **5** was converted to 2-(2-carbamoylphenyl)-3-methylisocarbostyril (**6**) by treatment with alkaline hydrogen peroxide. The ring closure of **6** to **2** was achieved under reflux in acetic acid containing boron trifluoride etherate.

The infrared (IR) spectrum of **2** exhibited a carbonyl stretching band at 1638 cm^{-1}. The nuclear magnetic resonance (NMR) spectrum showed a sharp singlet due to methyl protons at

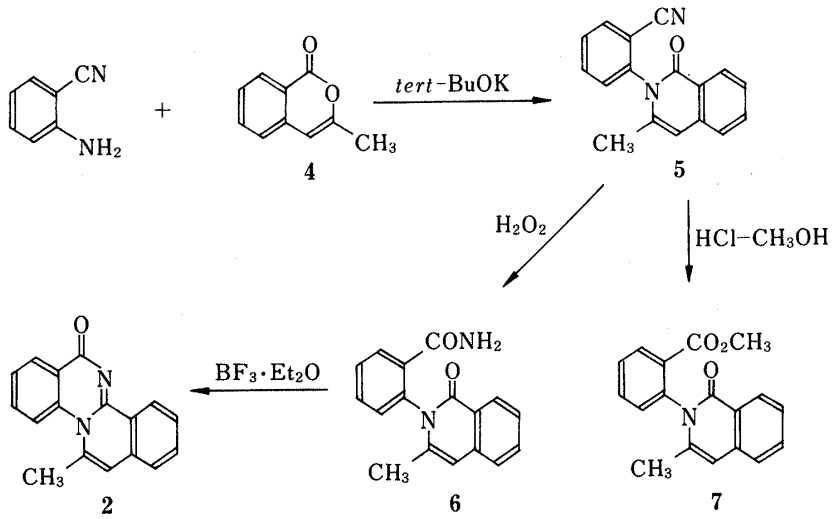


Chart 2

δ 2.70 (3H) and two characteristic multiplets of the protons at the 7-position and 4-position at δ 8.20—8.50 (1H) and 8.70—9.00 (1H). These three signals were shifted downfield compared with those of usual aromatic methyl protons or aromatic protons due to the deshielding effect of the aromatic ring or carbonyl group at the 6-position.

Butler[5] attempted the synthesis of the quinazolino[3,4-*a*]quinazolinone ring system from 3-(2-carbamoylphenyl)-4(3*H*)-quinazolinone, but was unable to prepare the starting material. In connection with the synthesis of **3a**, it seemed of interest to study the reaction of 2-methyl-4*H*-3,1-benzoxazin-4-one (**8a**) with 2-cyanoaniline, since the reaction of **8a** with anilines is known to be a convenient method for the preparation of 3-aryl-4-(3*H*)-quinazolinones, and extensive studies on the reaction mechanism have revealed that this reaction generally proceeds through an amidine type intermediate.[6] In the reaction of **8a** with 2-cyanoaniline, however, two different courses of reaction might take place from the amidine intermediate **9a** (X=Y=H, R=CH_3) which was assumed to be generated. One is attack of the amidine nitrogen atom on the carboxylic acid site in the usual manner to give 3-(2-cyanophenyl)-4(3*H*)-quinazolinone **10a** (X=Y=H, R=CH_3) (path A), which would be converted to **3a** by the method described for the synthesis of **2**. The other is attack at the nitrile site (path B). In this case, the product would be the 4-iminoquinazoline **12a** (X=Y=H, R=CH_3), which should be cyclized to **3a** under mild conditions. Cyclization through similar imino intermediates has been reported in the synthesis of pyrazolo-,[7] thiadiazolo-[8] and triazoloquinazolinones.[9] If the latter course proceeds preferentially, the desired **3a** could be expected to be obtained in one pot.

When a solution of **8a** and 2-cyanoaniline in benzene was refluxed for 24 h, a crystalline product was obtained in 76.6% yield. The melting point (227—230 °C) of this product did not coincide with that of **10a** (mp 165—166 °C) which had been reported by Harrison.[10]

This product was identified as **3a** on the basis of elementary analysis, spectral data, and chemical reaction. The elemental analysis indicated the empirical formula $C_{16}H_{11}N_3O$ and the mass spectrum (MS) showed the parent peak at *m/e* 261. These results indicate that the compound corresponds to a dehydrated product of the one-to-one adduct of **8a** and 2-cyanoaniline. The IR spectrum showed a carbonyl stretching band at 1665 cm^{-1} and the absence of any characteristic absorption owing to a nitrile group. The NMR spectrum exhibited a singlet at δ 3.00 (3H) due to the methyl group and three multiplets at δ 7.27—7.96 (6H), 8.18—8.48 (1H), and 8.50—8.74 (1H) assignable to aromatic protons. This signal pattern resembles that of **2**. Further evidence in support of the structure **3a** was provided by

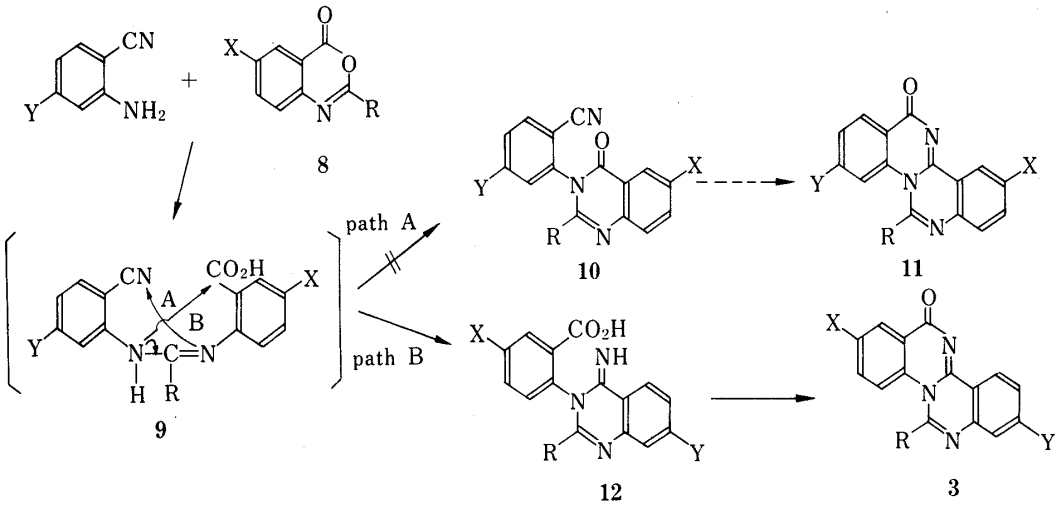


Chart 3

the following chemical reaction. Compound **3a** was readily hydrolyzed in dilute hydrochloric acid at room temperature to give 2-(2-acetamidophenyl)-4(3*H*)-quinazolinone (**13**), whose melting point and spectral data were identical with those of the authentic sample.[11]

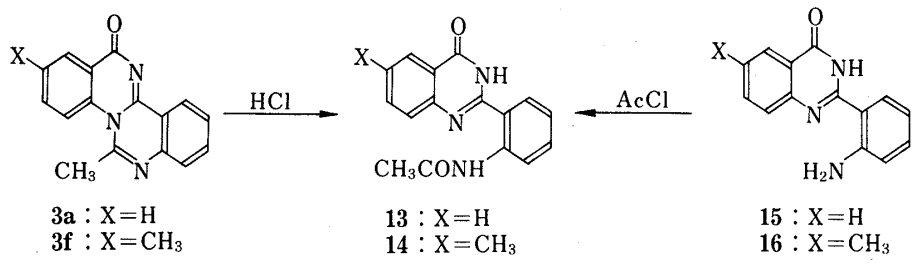


Chart 4

In order to investigate the formation pathway of the quinazolino[3,4-*a*]quinazolinone **3**, we examined the reaction of the substituted 4*H*-3,1-benzoxazin-4-ones **8** with 5-substituted-2-cyanoanilines. The results are summarized in Table I.

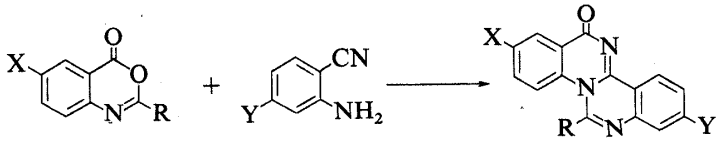
Treatment of 2,6-dimethyl-4*H*-3,1-benzoxazin-4-one (**8e**) with 2-cyanoaniline gave 2,6-dimethyl-13*H*-quinazolino[3,4-*a*]quinazolin-13-one (**3f**). The position of the methyl function in **3f** was determined chemically. Thus, **3f** was hydrolyzed to 2-(2-acetamidophenyl)-6-methyl-4(3*H*)-quinazolinone (**14**), whose melting point and spectral data were identical with those of an authentic sample prepared from 2-(2-aminophenyl)-6-methyl-4(3*H*)-quinazolinone (**16**).[12] If the reaction of **8e** with 2-cyanoaniline proceeds *via* path A, the product should be 6,10-dimethyl-13*H*-quinazolino[3,4-*a*]quinazolin-13-one (**11f**). Thus, the formation reaction of quinazolino-quinazolinones was concluded to proceed *via* path B.

Most of compounds **2** and **3** showed potent antiinflammatory activity. However, we could not find a compound having more potent activity than **1**.

Experimental

All melting points were determined on a Yamato MP-21 apparatus and are uncorrected. IR spectra were determined using a Shimadzu IR-27G spectrometer. NMR spectra were recorded on a Hitachi-Perkin Elmer R-20A instrument using TMS as an internal standard. Mass spectra were measured with a Hitachi M-60 mass spectrometer. Column chromatography was carried out on silica gel (Kieselgel 60, 0.063—0.200 mm, E. Merck).

TABLE I. 13*H*-Quinazolino[3,4-*a*]quinazolin-13-ones



8 **3**

Compd.	X	Y	R	mp (°C)	Yield (%)	Recryst. solvent	Formula	Analysis (%) Calcd (Found)			
								C	H	Cl	N
3a	H	H	CH_3	227—230	77	DMF	$C_{16}H_{11}N_3O$	73.55	4.24		16.08
								(73.41	4.04		16.19)
3b	H	CH_3	CH_3	209—210	76	DMF	$C_{17}H_{13}N_3O$	74.16	4.76		15.26
								(74.01	4.70		15.17)
3c	H	Cl	CH_3	223—225	74	DMF	$C_{16}H_{10}ClN_3O$	64.98	3.41	11.99	14.21
								(64.98	3.31	11.86	14.18)
3d	H	H	Isopr	190—192	55	EtOH	$C_{18}H_{15}N_3O$	74.72	5.23		14.53
								(74.75	5.16		14.38)
3e	H	H	Pro	165—167	69	EtOH	$C_{18}H_{15}N_3O$	74.72	5.23		14.53
								(74.77	5.19		14.50)
3f	CH_3	H	CH_3	239—241	80	DMF	$C_{17}H_{13}N_3O$	74.16	4.76		15.26
								(74.13	4.71		15.06)
3g	Cl	H	CH_3	252—254	75	DMF	$C_{16}H_{10}ClN_3O$	64.98	3.41	11.99	14.21
								(65.20	3.31	11.95	14.24)

3-Methylisocoumarin (4)[13]——A mixture of (2-carboxyphenyl)acetone[2] (11.5 g, 0.065 mol) and $SOCl_2$ (50 ml) was stirred at room temperature for 1 h. $SOCl_2$ was evaporated off *in vacuo*. The residue was washed with petroleum ether and collected by filtration to give **4** (7.0 g, 67.3%), mp 71—72 °C (lit. mp 73—74 °C). IR ν_{max}^{Nujol} cm^{-1}: 1720. NMR ($CDCl_3$) δ: 2.29 (3H, s), 6.22 (1H, s), 7.17—7.79 (3H, m), 8.07—8.30 (1H, m).

2-(2-Cyanophenyl)-3-methylisocarbostyril (5)——A solution of 2-cyanoaniline (3.6 g, 0.03 mol) and *tert*-BuOK (3.4 g, 0.03 mol) in THF (30 ml) was stirred at room temperature for 10 min. A solution of **4** (4.8 g, 0.03 mol) in THF (30 ml) was then added, and the whole was stirred at room temperature for 30 min. The mixture was neutralized with 10% HCl and extracted with $CHCl_3$. The extract was washed with H_2O, dried over $MgSO_4$ and concentrated *in vacuo* to give **5** (2.6 g, 33.3%), mp 159—162 °C. Recrystallization from 2-propanol gave **5** as colorless prisms, mp 164—165 °C. IR ν_{max}^{Nujol} cm^{-1}: 2220, 1680, 1621, NMR ($CDCl_3$) δ: 2.05 (3H, s), 6.56 (1H, s), 7.30—8.04 (7H, m), 8.31—8.60 (1H, m). MS *m/e*: 260 (M^+). *Anal.* Calcd for $C_{17}H_{12}N_2O$: C, 78.44; H, 4.65; N, 10.76. Found: C, 78.12; H, 4.61; N, 10.62.

2-(2-Methoxycarbonylphenyl)-3-methylisocarbostyril (7)——Hydrogen chloride was bubbled into a solution of **5** (0.2 g, 0.77 mmol) in MeOH (15 ml) under cooling in ice-water for 30 min. The solution was refluxed for 20 h, then concentrated *in vacuo*, neutralized with aqueous $NaHCO_3$ and extracted with $CHCl_3$. The extract was dried over $MgSO_4$ and concentrated *in vacuo*. The residue was subjected to silica gel column chromatography (5 g) using $CHCl_3$ to give **7** (0.07 g), mp 150—153 °C. IR ν_{max}^{Nujol} cm^{-1}: 1728, 1658, 1622. NMR ($CDCl_3$) δ: 2.03 (3H, s), 3.75 (3H, s), 6.58 (1H, s), 7.28—8.10 (6H, m), 8.20—8.67 (2H, m). MS *m/e*: 293 (M^+). *Anal.* Calcd for $C_{18}H_{15}NO_3$: C, 73.70; H, 5.15; N, 4.78. Found: C, 73.61; H, 5.09; N, 4.61.

2-(2-Carbamoylphenyl)-3-methylisocarbostyril (6)——H_2O_2 (35%) (10 ml) was added to a solution of **5** (2.3 g, 0.0088 mol) and KOH (0.56 g, 0.01 mol) in EtOH (50 ml) at 50 °C. After being stirred at 50 °C for 1 h, the mixture was concentrated *in vacuo*. The residue was neutralized with 10% HCl and extracted with $CHCl_3$. The extract was dried over $MgSO_4$ and concentrated *in vacuo* to give **6** (2.0 g, 81.3%), mp 186—189 °C. Recrystallization from 2-propanol gave **6** as colorless prisms, mp 190—191 °C. IR ν_{max}^{Nujol} cm^{-1}: 3380, 3160, 1657, 1620. NMR ($CDCl_3$) δ: 2.00 (3H, s), 5.73 (1H, br), 6.47 (1H, s), 6.77 (1H, br), 6.99—7.80 (7H, m), 8.10—8.50 (1H, m). *Anal.* Calcd for $C_{17}H_{14}N_2O_2$: C, 73.36; H, 5.07; N, 10.07. Found: C, 73.12; H, 4.97; N, 10.05.

12-Methyl-6*H*-isoquino[2,1-*a*]quinazolin-6-one (2)——A solution of **6** (1.8 g, 0.0065 mol) and $BF_3 \cdot Et_2O$ (5 ml) in AcOH (30 ml) was refluxed for 8 h, then the solvent was evaporated off *in vacuo*. The residue was neutralized with aqueous $NaHCO_3$ and extracted with $CHCl_3$. The extract was dried over $MgSO_4$ and concentrated *in vacuo* to give **2** (0.7 g, 41.6%), mp 205—208 °C. Recrystallization from 2-propanol gave **2** (0.56 g) as colorless prisms, mp 208—

209 °C. IR ν_{max}^{Nujol} cm^{-1}: 1638, 1601. NMR ($CDCl_3$) δ: 2.70 (3H, s), 6.84 (1H, s), 7.29—7.90 (6H, m), 8.20—8.50 (1H, m), 8.70—9.00 (1H, m). *Anal.* Calcd for $C_{17}H_{12}N_2O \cdot 1/2H_2O$: C, 75.82; H, 4.87; N, 10.40. Found: C, 75.91; H, 4.58; N, 10.30.

4*H*-3,1-Benzoxazin-4-ones (8)——2-Methyl-(**8a**),[6] 2-isopropyl-(**8b**),[14] 2-propyl-(**8c**),[15] 6-chloro-2-methyl-(**8d**)[16] and 2,6-dimethyl-4*H*-3,1-benzoxazin-4-one (**8e**)[17] were prepared according to the reported methods.

2-Cyanoanilines——5-Chloro-[18] and 5-methyl-2-cyanoaniline[19] were prepared according to the reported methods.

General Procedure for Preparation of 13*H*-Quinazolino[3,4-*a*]quinazolin-13-ones (3) [Table I]. A Typical Example: 6-Methyl-13*H*-quinazolino[3,4-*a*]quinazolin-13-one (3a)——A solution of **8a** (4.83 g, 0.03 mol) and 2-cyanoaniline (3.54 g, 0.03 mol) in benzene (50 ml) was stirred at the reflux temperature for 24 h. The mixture was then cooled to give a crystalline product (6.0 g, 76.6%) mp 227—230 °C. The product was recrystallized from DMF to give **3a** (4.0 g), mp 227—230 °C. IR ν_{max}^{Nujol} cm^{-1}: 1665, 1620, 1605. NMR (DMSO-d_6) δ: 3.00 (3H, s), 7.27—7.96 (6H, m), 8.18—8.48 (1H, m), 8.50—8.74 (1H, m). MS *m/e*: 261 (M^+).

2-(2-Acetamidophenyl)-4(3*H*)-quinazolinone (13)——A mixture of **3a** (0.43 g, 0.0016 mol) and 10% HCl (2 ml) in EtOH (10 ml) was stirred at room temperature for 30 min. The precipitate that had formed was collected by filtration to give **13** (0.3 g), mp 260—265 °C. Recrystallization from DMF gave **13**, mp 274—275 °C. The IR spectrum of the product was identical with that of an authentic sample prepared by Butler's method.[5]

2-(2-Acetamidophenyl)-6-methyl-4(3*H*)-quinazolinone (14)——Method A: By a procedure similar to that described for the preparation of **13**, reaction of **3f** (0.5 g) and 10% HCl (5 ml) in EtOH (5 ml) gave **14** (0.4 g), mp >280 °C. Recrystallization from DMF gave a pure sample, mp >280 °C. IR ν_{max}^{Nujol} cm^{-1}: 3200—3100, 1678, 1621, 1604. NMR (CF_3COOD) δ: 2.30 (3H, s), 2.67 (3H, s), 7.49—8.13 (6H, m), 8.36 (1H, s). *Anal.* Calcd for $C_{17}H_{15}N_3O_2$: C, 69.61; H, 5.15; N, 14.33. Found: C, 69.37; H, 5.03; N, 14.21.

Method B: AcCl (0.1 g) was added to a stirred solution of 2-(2-aminophenyl)-6-methyl-4(3*H*)-quinazolinone[11] (**16**, 0.215 g, 0.001 mol) in pyridine (5 ml). After being stirred at room temperature for 1 h, the mixture was poured into ice-water (50 ml) to give **14** (0.2 g), mp >280 °C. The spectral data of the product were identical with those of **14** prepared by Method A.

Acknowledgement The authors wish to thank Drs. I. Chibata, M. Miyoshi, M. Kizumi and N. Yoneda for their encouragement throughout this work.

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