Studies on Furan Derivatives. X [1]. Preparation of 2-Methylfuro[2,3-*c*]quinoline Derivatives

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4-Chloro-2-methylfuro[2,3-*c*]quinoline (IV) was synthesized from ethyl 3-(2-nitrophenyl)-5-methyl-2-furoate and IV was allowed to react with some nucleophiles to afford the corresponding 4-substituted 2-methylfuro-[2,3-*c*]quinoline derivatives, respectively. On treatment of IV with potassium azide in dimethylsulfoxide, 2-methylfuro[2,3-*c*]tetrazolo[1,5-*a*]quinoline was formed path azido-tetrazolo isomerization. 2-Methylfuro-[2,3-*c*]quinoline was prepared by the reduction of IV.

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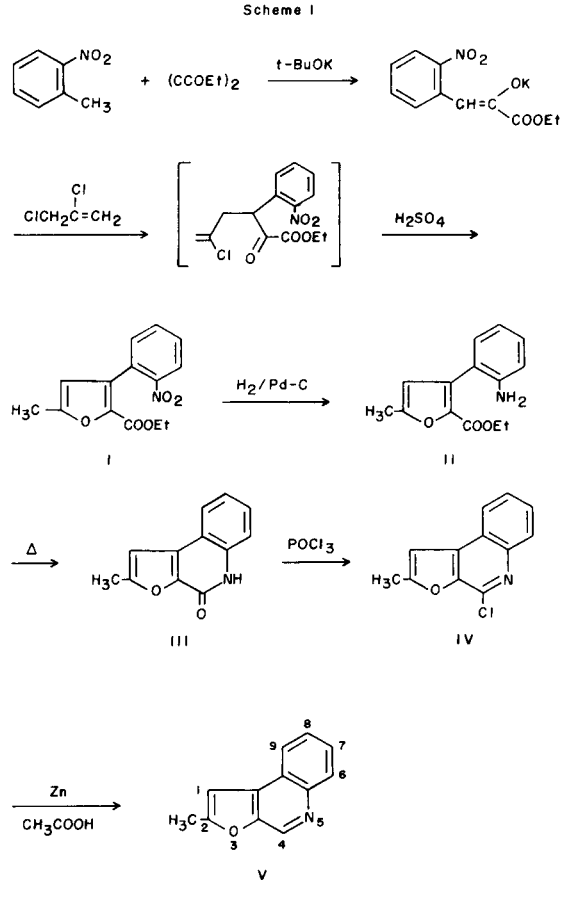
It is possible to design the various types of furoquinolines by fusion of the furan and the quinoline ring. Since it was found that the quinoline alkaloides, such as dictamine isolated from some plants of the *Rutaceae* exhibit a variety of biological activities, the principal current research in this ring system is the synthesis, reaction and evaluation of furo[2,3-*b*]quinoline derivatives [3]. On the other hand, the other furoquinoline ring systems have also been investigated by a number of workers [4-11].

In the present paper, with the synthesis of new furo-condensed ring derivatives with some biological activity as the objective, the preparation of the hitherto unknown furo[2,3-*c*]quinoline is described. In the literature, there is a short description of the synthesis of furo[2,3-*c*]quinolin-4-ones by photochemical oxidative cyclization of furan-2-carboxanilides [12,13]. However, an alternative route to furo[2,3-*c*]quinolin-4-ones needs to be developed, since the quantitative limitation is recognized in using furo[2,3-*c*]-quinolin-4(5*H*)-ones, as the starting material, which is prepared by the photolytic method. Thus, ethyl 3-(2-nitrophenyl)-2-furoates seemed to be prefered to prepare furo[2,3-*c*]quinolin-4-(5*H*)-ones, because the binding between the amino group formed by reduction of its nitro group and the ester group in these compounds seems to be easy.

Gosteli [14] has reported the preparation of ethyl 2-(3-chloro-2-nitrophenyl)-5-methyl-2-furancarboxylate from 3-chloro-2-nitrotoluene in the synthetic researches of the antibiotic, pyrrolnitrin. Therefore, first, ethyl 5-methyl-3-(2-nitrophenyl)-2-furancarboxylate (I) was prepared according to Gosteli's method as shown in Scheme 1. The condensation of *o*-nitrotoluene with diethyl oxalate in the presence of potassium *t*-butoxide, quantitatively gave the potassium salt of ethyl 2-nitrophenylpyruvate. The potassium salt was allowed to react with 2,3-dichloropropene to afford ethyl 2-oxo-3-(2-nitrophenyl)-5-chloro-5-hexenoate as an oily substance. When the oil was treated with sulfuric acid, I was obtained in 38% yield as yellow prisms. An attempt to use a one-step ring-closure of **1** which had been successful in cyclizing ethyl 2-nitrocinnamate into quinolines [15,16] proved unsuccessful with **1** in our hands. Thus the expected 4-ethoxy-2-methylfuro[2,3-*c*]-quinoline was not obtained from the reaction of I. Only two unknown crystalline substances were isolated.

Next, a preparative course *via* the lactam was investigated. Thus, catalytic hydrogenation of I over palladium-charcoal in ethanol was carried out to give ethyl 5-methyl-3-(2-aminophenyl)-2-furancarboxylate (II) in quantitative yield. The structure of II was confirmed by

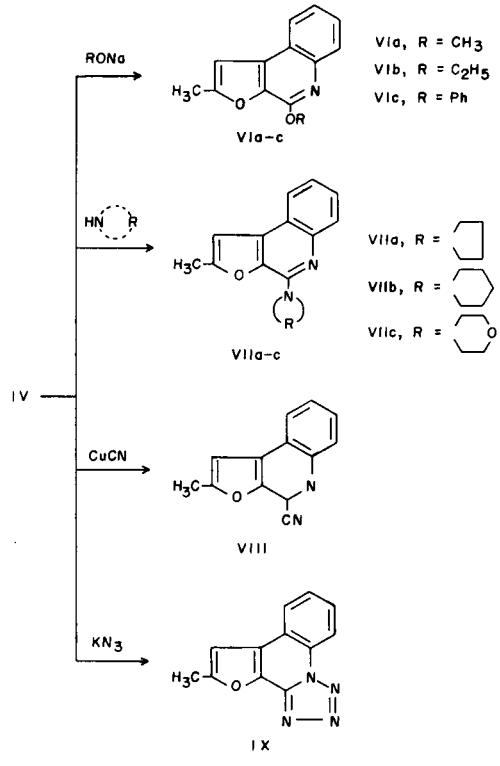
Scheme I



the presence of two absorption bands due to a primary amine at 3375 and 3470 cm^{-1} in the ir spectrum, however, II was difficult to purify because of instability to heat. Compound II was gradually cyclized to 2-methylfuro-[2,3-*c*]quinolin-4-(5*H*)-one (III) on standing in air to give colorless needles, mp 274-275°. The cyclization was accelarated by reflux in aprotic solvents such as benzene or petroleum ether to give III in 88% yield. The ir spectrum of III showed an absorption band attributed to a lactam carbonyl at 1690 cm^{-1} and the nmr spectrum showed the following signals, δ 7.07 (1H, s, C_1-H), 7.15-8.10 (4H, m, C_{6-9}-H), 2.53 (3H, s, CH_3), 11.70 (1H, broad s, NH). The elemental analytical value of III agreed with a molecular formula of $C_{12}H_9NO$.

The lactam III was converted into the corresponding 4-chloro-2-methylfuro-[2,3-*c*]quinoline (IV) by chlorination with phosphoryl choride in a sealed tube. Compound IV is the first aromatized derivative obtained in this ring system. Reduction of IV with zinc-acetic acid furnished 2-methylfuro[2,3-*c*]quinoline (V) in 60% yield. In the nmr spectrum of V, the singlet of C_4-H was observed at 9.03 ppm. Since it is expected that the chlorine atom at the 4-position of IV is activated towards nucleophilic substitutions, the reaction of 2-methylfuro[2,3-*c*]quinoline with some nucleophiles was carried out in order to obtain new derivatives as shown in Scheme 2. The reaction of IV with sodium methoxide or ethoxide gave 4-methoxy- and 4-ethoxy-2-methylfuro[2,3-*c*]quinoline (VIa and IVb) in good yields. Treatment of IV with potassium phenoxide in dimethyl sulfoxide at 100° gave 2-methyl-4-phenxoyfuro-[2,3-*c*]quinoline (VIc) in 13% yield with the recovery of 50% of IV. It is known that many 2-aminoquinolines have various pharmacological activities [17]. Consequently, IV was allowed to react with alicyclic amines (pyrrolidine, piperidine and morpholine) to afford the corresponding 4-amino-2-methylfuro[2,3-*c*]quinolines VIIa-c in good yields. The physical and spectral data of VIa-c and VIIa-c listed in Table I and II.

Scheme 2



Cyanation of IV was not accomplished with sodium or potassium cyanide, but substitution was achieved by the use of copper(I) cyanide to give 4-cyano-2-methylfuro-[2,3-*c*]quinoline (VIII), mp 205° as colorless prisms in 42% yield. An absorption band at 2250 cm^{-1} in the ir spectrum of VIII indicated the presence of a nitrile group.

The reaction of IV with potassium azide in dimethyl sulfoxide was very slow, therefore the reaction rate was im-

Table I

4-Substituted 2-Methylfuro[2,3-*c*]quinolines VIa-c and VIIa-c

Compound No.	Yield (%)	Mp (°C)	Appearance Recrystallization	Formula	Analysis (%) Calcd. (Found) C	H	N
VIa	88	54.5-55.5	Colorless prisms Petroleum ether	$C_{13}H_{11}NO_2$	73.22 (72.95)	5.20 (5.10)	6.57 (6.62)
VIb	97	94-95.5	Colorless plates Petroleum ether	$C_{14}H_{13}NO_2$	73.99 (74.12)	5.77 (5.59)	6.16 (6.00)
VIc	13	109-110	Colorless bars Petroleum benzin	$C_{18}H_{13}NO_2$	78.53 (78.43)	4.76 (4.78)	5.09 (5.22)
VIIa	86	107-109	Colorless needles Petroleum benzin	$C_{16}H_{16}N_2O$	76.16 (76.02)	6.39 (6.52)	11.10 (11.00)
VIIb	82	93-94	Colorless prisms Petroleum ether	$C_{17}H_{18}N_2O$	76.66 (76.56)	6.81 (7.01)	10.52 (10.43)
VIIc	78	110-111	Colorless prisms Petroleum ether	$C_{16}H_{16}N_2O_2$	71.62 (71.55)	6.01 (5.92)	10.44 (10.58)

Table II

Spectral Data for 4-Substituted 2-Methylfuro[2,3-*c*]quinolines VIa-c and VIIa-c

Compound No.	MS m/e (M^+)	UV λ Max (ethanol) nm	NMR [a], δ (acetone-d_6) F(b)-H	F [b] -CH_3	B [C] -H	Other signals
VIa	213	232, 255	7.05	2.57	7.30-8.20	4.18
		433, 448	(1H, d, J = 1 Hz)	(3H, d, J = 1 Hz)	(4H, m)	(3H, s, OCH_3)
VIb	227	233, 251	7.08	2.57	7.30-8.20	1.50, 4.67
		435	(1H, d, J = 1 Hz)	(3H, d, J = 1 Hz)	(4H, m)	(5H, t and q, J = 7 Hz, CH_2CH_3)
VIc	275	232, 248	7.16	2.61	7.20-8.30	7.38
		433	(1H, d, J = 1 Hz)	(3H, d, J = 1 Hz)	(4H, m)	(5H, broad s, phenyl H)
VIIa	254	229, 276	6.91	2.46	7.10-8.00	1.85-2.10, 3.70-4.10
		287, 315	(1H, d, J = 1 Hz)	(3H, d, J = 1 Hz)	(4H, m)	(8H, each m, pyrrolidino H)
VIIb	266	230, 278	6.96	2.53	7.10-8.10	1.55-2.00, 3.75-4.20
		290, 317	(1H, d, J = 1 Hz)	(3H, d, J = 1Hz)	(4H, m)	(10H, each broad s, piperidino H)
VIIc	268	230, 277	7.00	2.54	7.10-8.10	3.70-4.10
		288, 316	(1H, d, J = 1 Hz)	(3H, d, J = 1 Hz)	(4H, m)	(8H, broad s, morpholino H)

[a] s = singlet, d = doublet, m = multiplet, q = quartet, t = triplet. [b] F = Furan ring. [c] B = Benzene ring.

proved by the addition of a catalytic amount of Crown ether to yield IX, mp 234-236° as colorless leaves in 65% yield. The mass spectrum of IX showed a molecular ion peak at m/z 224 which corresponded to the mass number expected of 4-azido-2-methylfuro[2,3-*c*]quinoline but the ir spectrum of IX did not show the band on an azido group. Also, the nmr spectrum of IX revealed the presence of the original ring system and the elemental analytical value of IX agreed with a molecular formula $C_{12}H_8N_2O$. It is well known that if the azido group is attached to the carbon atom adjacent to an annular nitrogen atom of a heterocyclic ring, it may spontaneously cyclize to give a fused tetrazole ring [18,19]. In general the transformation of a nitrogen-containing heterocyclic azido compound into a tetrazole compound has been interpreted as an azido-tetrazole isomerization. Accordingly, the structure of IX was assigned as 2-methylfuro[2,3-*c*]tetrazolo[1,5-*a*]quinoline.

It has been reported that azido-tetrazole isomerization is influenced by the polarity of solvent and temperature. However, the reaction of IV with potassium azide only gave the tetrazolo form rather than its azido form.

The biological activities of the derivatives mentioned above are now in progress.

EXPERIMENTAL

All melting points are uncorrected. The following instruments were used for obtaining the physical data: nmr spectra (TMS as internal standard): JEOL JNM-60-HL and PS-100; ir spectra: JASCO IRI-1; uv spectra: JASCO UVIDEC-1; mass spectra(direct solid inlet): Shimadzu LKB-9000. Column chromatography was carried out on silica gel (Wako gel C-200).

Ethyl 5-Methyl-3-(2-nitrophenyl)-2-furancarboxylate (I).

To a stirred solution of 10 g (73 mmoles) of *o*-nitrotoluene and 13.9 g (95 mmoles) of diethyl oxalate in 50 ml of absolute toluene, 10.6 g (95 mmoles) of potassium *t*-butoxide was added within five minutes. After the addition, stirring was continued for one hour at 70° and then the precipitate was collected. The product was washed with 50 ml of toluene and 50 ml of hexane, and recrystallized from acetone to afford reddish brown needles of the potassium salt of ethyl 2-nitrophenylpyruvate 18.0 g (90%). A mixture of 10.0 g (36 mmoles) of the potassium salt obtained above, 4.4 g (40 mmoles) of 2,3-dichloropropene, 1.5 g (10 mmoles) of sodium iodide, and 50 ml of hexamethylphosphortriamide was stirred for three hours at room temperature, poured into ice water and extracted with ether. The ether extract was washed with water three times, dried over anhydrous magnesium sulfate, and evaporated down to give an orange oil. Fifty ml of concentrated sulfuric acid was added to the oil with ice-cooling and the mixture was stirred for two hours at room temperature and poured onto crushed ice. The precipitate was filtered and recrystallized from petroleum ether to give yellow crystals of I, 3.8 g (38% from the potassium salt), mp 99-101°; ir (nujol): ν max 1710 cm^{-1} (C=O), 1355 and 1530 cm^{-1} (NO_2); nmr (deuterioacetone): δ 6.38 (1H, d, J = 1.0 Hz, furan ring 4-H), 7.40-8.20 (4H, m, nitrophenyl H), 2.42 (3H, d, J = 1.0 Hz, CH_3), 1.10, 4.09 (5H, t and q, J = 7.0 Hz, CH_2CH_3).

Anal. Calcd. for $C_{14}H_{13}NO_5$: C, 61.09; H, 4.76; N, 5.09. Found: C, 60.91; H, 4.58; N, 5.02.

2-Methylfuro[2,3-*c*]quinolin-4(5*H*)-one (III).

A solution of 15.0 g (55 mmoles) of I in 450 ml ethanol was hydrogenated in the presence of 5% palladium-charcoal. After 3665 ml of hydrogen was absorbed, the catalyst was filtered off, and the solvent was removed *in vacuo* to afford II as an orange oil in quantitative yield. Compound II was then dissolved in benzene or in petroleum ether and boiled under reflux for ten hours. After cooling, the precipitate was collected and recrystallized from methanol to afford colorless needles of III, 9.5 g (88% from I), mp 274-275°; ms: m/z 199 (M^+); ir (nujol): ν max 1690 cm^{-1} (C=O); nmr (deuteriodimethylsulfoxide): δ 7.07 (1H, s, C_1-H), 7.15-8.10 (4H, m, $C_{6,9}$-H), 2.53 (3H, s, CH_3), and 11.70 (1H, broad s, NH).

Anal. Calcd. for $C_{12}H_9NO_2$: C, 72.35; H, 4.55; N, 7.03. Found: C, 72.01; H, 4.67; N, 7.24.

4-Chloro-2-methylfuro[2,3-*c*]quinoline (IV).

A solution of 5.0 g (25 mmoles) of III in 50 ml of phosphoryl chloride was heated in a sealed tube at 180° for five hours. After cooling the reaction mixture was poured into ice-water and the precipitate was collected. Recrystallization from petroleum ether gave colorless prisms IV, 4.5 g (82%), mp 129-131°; ms: m/z 217 (M^+), 219 (M^++2); nmr (deuterioacetone): δ 7.50-8.30 (4H, m, $C_{6,9}$-H), 7.19 (1H, d, J = 1.0 Hz, C_1-H), 2.63 (3H, d, J = 1.0 Hz, CH_3).

Anal. Calcd. for $C_{12}H_8ClNO$: C, 66.22; H, 3.71; N, 6.44. Found: C, 66.41; H, 3.45; N, 6.34.

2-Methylfuro[2,3-*c*]quinoline (V).

A mixture of 0.5 g (2.3 mmoles) of IV, 1.0 g of zinc powder and 10 ml of glacial acetic acid was refluxed for two hours with stirring. After cooling, the precipitate was filtered off and the filtrate was poured into ice water. The mixture was made strongly basic to litmus with 10% sodium hydroxide solution and extracted with ether. The ether extract was washed with water three times, dried over anhydrous sodium sulfate, and evaporated. The residue was chromatographed on silica gel with benzene as the eluant. This procedure yielded colorless prisms of V, 0.25 g (60%), mp 80-81°; ms: m/z 183 (M^+); ir (nujol): ν max 1560 cm^{-1} (C=N); nmr (deuterioacetone): δ 2.59 (3H, d, J = 1.0 Hz, CH_3), 7.13 (1H, d, J = 1.0 Hz, C_1-H), 7.50-7.90, 8.00-8.35 (4H, each m, $C_{6\text{-}9}$-H), 9.03 (1H, s, C_4-H).

Anal. Calcd. for $C_{12}H_9NO$: C, 78.67; H, 4.95; N, 7.65. Found: C, 78.99; H, 5.07; N, 7.53.

4-Methoxy-2-methylfuro[2,3-*c*]quinoline (VIa).

To a solution of 15 ml of absolute methanol containing 0.1 g (4.3 mg-atoms) of sodium, I was added. The mixture was refluxed for nine hours, poured into ice water and extracted with ether. The ether extract was washed with water three times, dried over anhydrous magnesium sulfate and evaporated. The residue was chromatographed on silica gel with benzene as the eluant. This procedure yielded colorless prisms of VIa, 0.26 g (88%), mp 54.0-55.5°.

4-Ethoxy-2-methylfuro[2,3-*c*]quinoline (VIb).

To a solution of 15 ml of absolute ethanol containing 0.1 g (4.3 mg-atoms) of sodium, 0.3 g (1.4 mmoles) of IV was added. The mixture was refluxed for one hour and poured into ice water. The precipitate was collected and recrystallized from petroleum ether to afford colorless plates of VIb, 0.3 g (97%), mp 94.0-95.5°.

2-Methyl-4-phenoxyfuro[2,3-*c*]quinoline (VIc).

A mixture of 0.3 g (1.4 mmoles) of IV, 0.2 g (1.7 mmoles) of sodium phenoxide and 15 ml of absolute dimethylsulfoxide was heated at 85° for five hours. After cooling, the mixture was poured into ice water and extracted with ether. The ether extract was washed three times with water, dried over anhydrous sodium sulfate and evaporated. The residue was chromatographed on silica gel with benzene as the eluant. This procedure yielded colorless prisms of VIc, 0.05 g (13%), mp 109-110°, with partial recovery of IV (50%).

4-Alicyclic Amino-2-methylfuro[2,3-*c*]quinolines VIIa-c.

A mixture of 0.3 g (1.4 mmoles) of IV and an excess of alicyclic amines (5.0 ml) was heated under reflux for three to five hours. After cooling, the mixture was poured into ice water and the precipitate was collected. Recrystallizations from suitable solvents gave VIIa-c in good yields (see Table I and II).

4-Cyano-2-methylfuro[2,3-*c*]quinoline (VIII).

A mixture of 0.3 g (1.4 mmoles) of IV, 0.14 g (1.5 mmoles) of cuprous cyanide and 15.0 ml of dimethylformamide was refluxed for six hours.

After cooling, the reaction mixture was filtered and the filtrate was poured into ice-water. The precipitate was filtered and chromatographed on silica gel with benzene as the eluant. This procedure yielded colorless prisms of VIII, 0.12 g (42%), mp 205° with partial recovery of IV (47%). Compound VIII had ms: m/z 208 (M^+); ir (nujol): ν max 2250 cm^{-1} (C=N); nmr (deuterioacetone): δ 7.70-8.50 (4H, m, $C_{6\text{-}9}$-H), 7.37 (1H, d, J = 1.0 Hz, C_1-H), 2.72 (3H, d, J = 1.0 Hz, CH_3).

Anal. Calcd. for $C_{13}H_8N_2O$: C, 74.99; H, 3.87; N, 13.46. Found: C, 74.78; H, 3.91; N, 13.09.

2-Methylfuro[2,3-*c*]tetrazolo[1,5-*a*]quinoline (IX).

A mixture of 0.3 g (1.4 mmoles) of IV, 0.2 g, (2.4 mmoles) of sodium azide, a catalytic amount of 18-Crown-6, and 15 ml of dimethylsulfoxide was heated at 90° for eight hours. After cooling, the mixture was poured into ice water and the precipitate was collected. Recrystallization from benzene gave colorless leaves of IX, 0.2 g (65%), mp 234-236°; ms: m/z 224 (M^+); ir (nujol): ν max 1630 cm^{-1} (C=N); nmr (deuteriochloroform): δ 2.67 (3H, d, J = 1.0 Hz, CH_3), 6.90 (1H, d, J = 1.0 Hz, C_1-H), 7.69-8.20, 8.50-8.90 (4H, each m, $C_{6\text{-}9}$-H).

Anal. Calcd. for $C_{12}H_8N_4O$: C, 64.29; H, 3.60; N, 24.99. Found: C, 64.11; H, 3.52; N, 24.87.

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