Synthesis of substituted quinolines and heterocyclo[x,y-c]quinolines by the nucleophilic substitution and rearrangements of 4-chloro-2-methyl-3-nitroquinolines

A. I. khodair, M. M. A. Abbasi, El-Sayed I. Ibrahim, A. H. Soliman and El-Sayed H. El-Ashry***

*Chemistry Department, Faculty of Science, Suez Canal University, Ismailia, *Tanta University, Tanta and **Alexandria university, Alexandria Egypt.*

Abstract:

4-Chloro-2-methyl-3-nitroquinolines **1-5** were used as precursors for the synthesis of heterocyclo[c]quinolines, where the nitro group plays different roles in the cyclization processes. Reduction of the 4-amino-3-nitro derivatives **6-10** to the 3,4-diaminoquinolines **11-14**, and subsequent condensation with carbonyl compounds gave the corresponding imidazo[4,5-c]quinolines **15-24.** Condensation of **1-5** with benzylamine or amino acids and subsequent cyclization gave the respective 3-hydroxy-2-phenylimidazo[4,5-c]quinolines **30-34**, and **35-43; 35** was cyclized to the imidazo[4,5-c]quinoline **44**. Heating the 4-azido-3-nitroquinaldine **45** in benzene gave 1,2,5-oxadiazolo[3,4-c]quinoline **46**. Reaction of **2-5** with, salicylaldehyde and salicylic acid gave **47-50** and **51-54,** respectively. Cyclization of either **47** or **51** and **48** or **52** gave the corresponding benzopyrano[3,2-c]quinolines **55** and **56**.

Introduction:

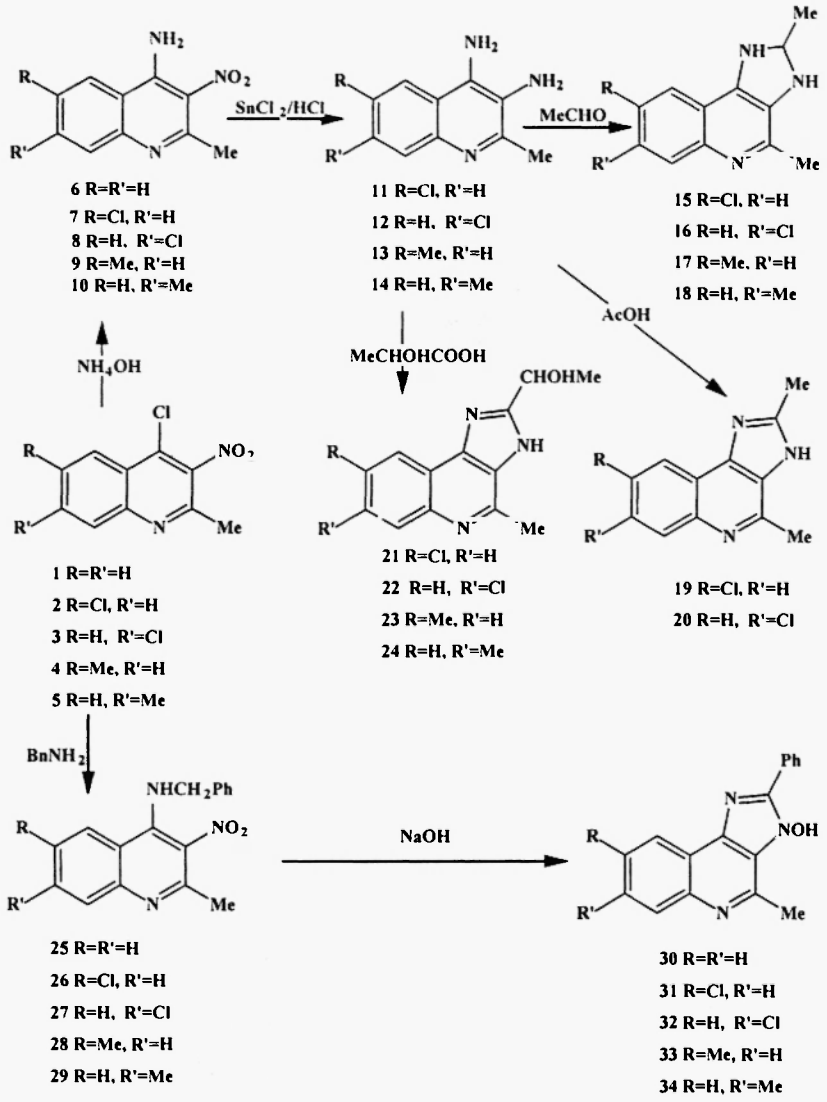
Quinoline derivatives display a wide variety of biological properties. Thus, the 3- and 4-amino derivatives, such as chloroquine and amodiaquine play a key role in the treatment of malaria [1-5] and the 3-amino acid derivatives are useful as antibacterial agents [6-9]. The 3-methyl sulphonyl derivatives are used in the treatment of heart failure and as antihypertensives [10-15]. Indoloquinolines show a remarkable potent activity as antitumor agents [16,17]. Thiazoloquinolines are useful as fungicides [18] and pyrazoquinolines act as antibacterials, potent immunostimulants and interlukine inhibitors [19-22]. Imidazoquinolines act on benzodiazepine receptors, inhibitors of acid secretion and bone resumption, bronchodialators , inhibitor of blood platelets and antibacterials [23-26].

The main objective in the present work is the synthesis of fused heterocycles on site *c* of the quinoline ring, which can be of potential chemotherapeutic value. The versatility of the 4-chloro-2-methyl-3-nitro-6 or 7-substitutedquinolines **1-5** as precursors for generating the bifunctionality required for building heterocyclic rings on side c of the quinoline ring has been explored, whereby three various approaches for the utilization of the nitro group has been used.

Results and Discussions

The high reactivity of the 4-position in 4-chloro-2-methyl-3-nitroquinolines **1-5**[27] towards nucleophilic reagents can be due to the presence of the adjacent 3-nitro group. Thus, using, ammonia as a nucleophile in the displacement of the chlorine atom in **1-5** led to the formation of the 4-amino-2-methyl-3-nitro-6 or7-substitutedquinoline derivatives **6-10**. The ^{1}H nmr spectrum of **6** showed a D_2O exchangeable singlet for the amino group at 3.5 ppm. Reduction of the nitro group with stannous chloride gave the corresponding 3,4-diamino derivatives **11-14** whose infrared spectra indicated the absence of the nitro group. The imidazoline ring could be generated from **11-14** by reaction with acetaldehyde to give 2,3-dihydro-2,4-dimethyl-7- or 8-substitutedimidazo[4,5-c]quinolines **15-18**. Condensation of **11** and **12** with acetic acid gave 7- or 8-chloro-2,4-dimethylimidazo[5,4-c]quinolines **19** and **20,** respectively. Reaction of **11-14** with lactic acid gave the respective 2-(1-hydroxyethyl)-4-methyl-7- or 8-substitutedimidazo[5,4-c]quinolines **21-24.** Condensation of 4-chloro-3-nitro-6- or 7-substituted quinolines **1-5** with benzylamine gave the corresponding 4-benzylamino derivatives **25-29**, which can be cyclized with sodium hydroxide to give 3-hydroxy-4-methyl-2-phenyl-7- or 8-substitutedimidazo[5,4-c]quinolines

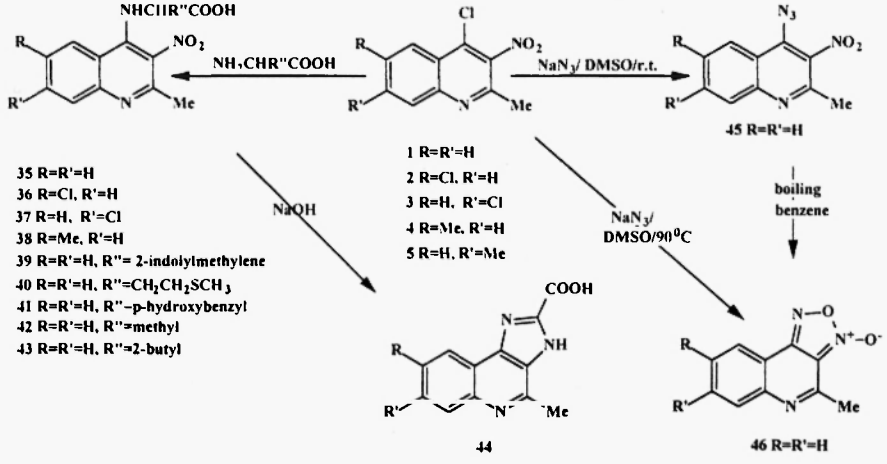
30-34. The ir spectra of **25-29** showed bands corresponding to the secondary amino and nitro groups which disappeared in the cyclized products **30-34** and showed instead bands at 3500 cm^{-1} due to the OH groups. The ^1H nmr spectra of **25-29** showed signals which can be due to the CH_2 and NH protons which disappeared in the cyclized compounds **30-34** confirming the cyclization process.



Scheme 1.

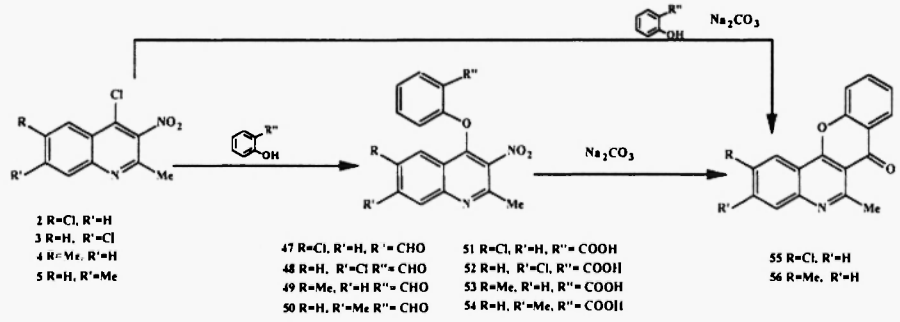
The 4-carboxymethylamino-3-nitro-6- or 7-substituted quinaldines **35-38** were prepared by the reaction of **6-10** with chloroacetic acid. Alternatively, they were prepared by condensation of **1-5** with glycine. Similarly, reaction of **1** with a series of amino acids, tryptophane, methionine, tyrosine alanine and isoleucine gave the corresponding 4-carboxysubstitutedmethylamino-3-nitro-6- or 7-substitutedquinaldines **39-43**. Cyclization of **35** by heating with sodium hydroxide afforded 2-carboxy-3-hydroxyimidazo[4,5-c]quinoline **44**. The structures were deduced from the combination of elemental analysis and spectroscopic data. the ^1H nmr spectral data of **35** showed a signal due to the CH_2 group which disappeared in the spectrum of **44**, thus confirming the cyclization process.

Reaction of **1** with sodium azide at room temperature gave the corresponding 4-azido derivative **45** which was cyclized during the crystallization from benzene to give 1.2,5-oxadiazolo[3,4-c]quinaldine **46**. Otherwise, **46** was obtained directly from the reaction of **1** with sodium azide on heating in DMF at 90°C. The infrared spectrum of the azide derivative **45** showed a characteristic band at 2080 cm^{-1} which disappeared in the spectrum of **46**. The mechanism of formation of **46** could be given as that reported for the cyclization of o-nitroazide derivatives [29].



Scheme 2.

The nitro group can be assessed as a leaving group. Thus, reaction of **2-5** with salicylic acid and salicylaldehyde gave 4-(2-formylphenoxy)-2-methyl-6- or 7-substitutedquinaldines(**47-50**) and 4-(2-carboxyphenoxy)-2-methyl-6- or 7-substituted- quinaldines (**51-54**), respectively. The ir spectra of **47-50** showed a carbonyl absorption band at 1690- 1680 cm^{-1} and of **51-54** the carboxyl carbonyl absorption at 1650- 1630 cm^{-1}. The mass spectrum of compound 47 showed the required molecular ion peak at m/z 342 and 344. The ^{1}Hnmr spectra of **47-50** showed signals at δ 10.3 (CHO), 7.7-6.7 (7H,Ar.), 3.0 (s,CH_3), 2.5 (s,CH_3) ppm . Compounds **51-54** showed a signal at: δ 10.2 ppm assigned for the carboxylic proton. Cyclization of either **47** or **51** afforded the same product, 2-chloro-6-methyl-7-oxobenzopyrano[3,2-c]quinolines **55**. Similarly, **48** or **52** were cyclized to 2,6-dimethyl-7-oxobenzopyrano[3,2-c]quinoline **56**. This could be explained by the loss of nitrite ion in case of **47** and **48** and nitrate ion in case of **51** and **52** to afford **55** and **56** respectively. Alternatively, **55** and **56** were directly prepared by reacting **2** and **4** with either salicaldehyde or salicylic acid in the presence of sodium carbonate. The ir spectra of **55** and **56** showed bands at 1690- 1680 cm^{-1}. characteristic for the carbonyl group.



Scheme 3

In conclusion, the 4-chloro-3-nitroquinolines are potential precursors for the synthesis of the fused heterocycles on the side c of the quinoline ring. This has been achieved by three different roles for the nitro group. First, its reduction to generate an o-diamine functionality which can be readily cyclized to the imidazolidine or imidazole rings. Secondly, its cyclization with a reactive methylene

group which can be at the 4- position to afford hydroxyimidazole rings. The third role is its use as a leaving group where benzopyrone moiety is formed.

EXPERIMENTAL

Melting points were uncorrected and were determined in glass capillary tubes on a MEL-TEMP II melting point apparatus. Microanalyses(table 1) were performed at the microanalytical laboratory at Cairo University. Infrared spectra were recorded on a Perkin-Elmer 1430 spectrophotometer with CDS data station using KBr Wafer technique. Nuclear magnetic resonance spectra were recorded on a Varian Gemini 200 MHz spectrometer. Mass spectra were run on a GC-MSQP 1000EX Schimadzu. The purity of the synthesized compounds were checked by TLC onglass plates coated with silica gel GF 254 type. The spots were detected by exposure to iodine vapor.

4-Chloro-2-methyl-3-nitro-6 or 7-substitutedquinolines (1-5):

A suspension of 4-hydroxy-2-methyl-3-nitro-6 or 7-substitutedquinolines (10 g, 0.0526 mole) in phosphorus oxychloride (100 ml) was heated gently on a boiling water bath with stirring until all the solid had dissolved. The excess of the oxychloride was removed under vacuum and the mixture was poured slowly with stirring onto ice cold ammonia (100 ml). The precipitated product was filtered, washed with dilute ammonia, water and dried. Recrystallization from either absolute ethanol or dry benzene gave the title compounds[27]. Mass spectra of compound **1**: m/z 222(21), 224(7), 176((31), 141(28), 140(100), 114(26), 113(22), 87(23), 75(28), 74(28) and **4**: m/z 236(30), 238(10), 22!(10), 191(40), 193(25), 160(7), 132(100), 63(50), 65(25). ^{13}C nmr of **1**: C2, 147; C3, 167; C4, 136; C4a, 125; C5, 126; C6, 119; C7, 125; C8, 133; C8a, 138; CH_3, 17 ppm

4-Amino-2-methyl-3-nitroquinolines (6-10)

A mixture of 4-chloro-2-methyl-3-nitroquinaldines **1-5** (0.0024 mole), ammonium hydroxide (25% solution, 10 ml.) and ethanol (10 ml) was heated under reflux for 3 hr. The mixture was concentrated and cooled. The precipitated product was filtered ,dried and recrystallized from ethanol to give the title compounds[28] (~ 75%). Ir showed bands at 3415-3328 cm^{-1} (NH_2),1555-1550 cm^{-1} (NO_2). Mass spectrum of 9: m/z 218(100), 204(30), 171(100), 142(60). 115(50), 92(80). ^{1}H nmr of compound 6:δ 8.3-7.5 (m.9H.Ar.), δ 3.5 (s,D2O ex., NH2), δ 2.5 (s,CH3). ^{3}C nmr spectrum of compound 6: C2, 47, C3, 118; C4, 153; C4a, 127, C5, 126; C6, 124; C7, 129; C8, 132; C8a, 146; CH3, 29 ppm.

3,4-Diamino-2-methyl-6 or 7-substitutedquinolines (11-14)

A hot solution of stannous chloride (25 g) in concentrated hydrochloric acid (25 ml) was added with vigorous stirring to a suspension of **6-10** (5 g) in acetic acid (50 ml). The mixture was heated on a water-bath for 1h., left overnight at room temperature and filtered. The filtrate was basified with sodium hydroxide solution, heated for 10 minutes and then extracted with chloroform. The extract was dried and evaporated to give the products, which were recrystallized from ethanol. Ir showed a broad band at 3550 -3100 cm^{-1} (NH_2)

2,3-Dihydro-2,4-dimethyl-7 or 8-substitutedimidazo[4,5-c]quinolines (15-18), 2,4-dimethyl-7 or 8-substitutedimidazo[4,5-c]quinolines (19-20) and **2-(1-hydroxyethyl)-4-methyl-7- or 8-substituted imidazo[4.5-c]quinolines (21-24)**

A mixture of the diaminoquinaldines **11-14** (0.00267 mole) and the carbonyl compounds (acetaldehyde, acetic acid or lactic acid) (0.027 mole) was heated on a water bath for 5h. The product was dissolved in ethanol and filtered. The filtrate was concentrated and cooled, and the formed precipitate was crystallized from ethanol to give the title compounds. Ir showed bands at 3550 - 3350 cm^{-1}. Mass spectrum of **20**: m/z 231(80), 233(26); 212(80), 214(80), 191(50), 193(22); 171(50), 151(55), 153(18); 131 (28), 107(50); 92(95), 94(32); 60(100), 62(20)

4-Benzylamino-2-methyl-3-nitro-6 or 7-substitutedquinolines (25-29):

A mixture of 4-chloro-3-nitroquinaldines **1-5** (0.002 mole), benzylamine (0.0045 mole) and dry benzene (20 ml) was heated under reflux for 3h., cooled and filtered. The filtrate was concentrated and cyclohexane (20 ml) was added. The precipitate was filtered off and recrystallized from cyclohexane to give the title compounds. Ir showed bands at 3430 - 3300 cm^{-1} (NH), 1555- 1550 cm^{-1} (NO_2). ^1H nmr of **25**: δ 8.5-7.3 (m,9H,Ar.) . δ 4.5(s,D2O exch. NH), δ 3.3 (s,CH_2), δ 2.7 ppm (s,CH_3). ^1H nmr of **29**: δ 8.5-7.2(m,9H,Ar), δ 4.4 (s,D2O exch. NH) . δ 2.7 (s,CH_2), δ 2.7 ppm (s,CH_3) ppm.

3-Hydroxy-4-methyl-2-phenyl-2H-imidazo[4,5-c]quinolines (30-34):

A mixture of **25-29** (0.00068 mole) and alcoholic sodium hydroxide (20% soln., 15 ml.) was heated under reflux for 6 hours. The mixture was poured onto cold water, neutralized with dilute hydrochloric acid. The formed precipitate was filtered off, washed with water and recrystallized from ethanol to give pale yellow crystals of the title compounds. Ir showed bands at 3550-345- cm^{-1}(OH). ^1H nmr of **34**: δ 8.0-7.2 (m,8H,Ar.), δ 4.0 (s,D_2O exch. OH), δ 2.8 (s,CH_3), δ 2.4 ppm (s,CH_3).

4-(N-Carboxymethylamino) and 4-(N-carboxysubstitutedmethylamino)-2-methyl-3-nitroquinolines (35-38) and (39-43):

a) A mixture of **1 - 5** (0.002 mole), amino acids (0.002 mole) and absolute ethanol (15 ml) was heated under reflux with stirring for 3h. The mixture was cooled, poured onto ice/water and basified with sodium carbonate solution. The precipitate was filtered off, washed with water, dried and recrystallized from ethanol.

b) A mixture of **6-10** (0.0053 mole), chloroacetic acid (0.5 g., 0.0053 mole) and ethanol (10 ml.) was heated on a water-bath for **4h**. The mixture was worked up as above to give products identical with that obtained by method (a). ir showed absorption bands at 3500 - 3300 cm^{-1}(OH), 1640 -1630 cm^{-1} (CO). ^1H nmr of **35**: δ 8.5(d,H8), δ 7.8(t,H7), δ 7.6(t,H6), δ 7.2(d,H5), δ 2.4(s,CH_3), δ 11.2 (s,COOH), δ 4.1(s,CH_2), δ 3.4(s,D2O ex., NH), δ 7.5(5H,Ar.) ppm. **39**: δ 8.3 (d,H8), δ 7.5(t,H7), δ 7.0 (t,H6), δ 7.3 (d,H5), δ 2.4 (s,CH_3), δ 11.0 (s,COOH), δ 4.3 (t,CH), δ 2.7 (d,CH_2), δ 3.7(s,D2O ex., NH), δ 7.5 (m.4H,Ar.) ppm. **40**: δ 8.6 (d,H8), δ 7.8 (t,H7), δ 7.6 (t,H6), δ 7.3 (d,H5), δ 2.0 (s,CH_3), δ 11.2 (s,COOH), δ 4.1 (t,CH), δ 2.6 (m,CH_2), δ 2.7 (t, CH_2), δ 3.4 (s,D2O ex., NH), δ 2.5 (s,CH_3) ppm.. **41**: δ 8.4 (d,H8), δ 7.8(τ,H7), δ 7.6 (τ,H6), δ 7.2 (d,H5), δ 11.0 (s,COOH), δ 4.2 (t,CH), δ 3.1 (d,CH_2), δ 3.4 (s,D2O ex., NH), δ 6.9 (m,4H,Ar.), δ 9.2 (s, D2O exch.OH) ppm. ^{13}C nmr **39:** 147, C2; 143,C3; 154,C4, 128,C4a; 126C5; 123,C6; 127,C7, 122,C8,145,C8a; 22,CH_3; 124, C1'; 109,C2'; 128,C3'; 119,C4'; 121,C5'; 118,C6'; 112,C7'; 134,C8'; 172,CO. **40:** 150, C2; 142,C3; 153,C4, 131,C4a; 126,C5; 124,C6; 129,C7, 131,C8, 146,C8a; 21,CH_3; 30, C1'; 31,C2'; 56,C3'; 173,CO, 15, SCH_3. **41** 151, C2; 142,C3; 154,C4, 124,C4a; 127C5; 126,C6; 129,C7, 132,C8, 147,C8a; 22,CH_3; 60, C1'; 26,C2'; 137,C3'; 115,C4'; 130,C5'; 156,C6'; 130,C7'; 115,C8'; 172,CO.

3-Hydroxy-4-methylimidazo[5,4-c]quinoline-2-carboxylic acid (44):

A mixture **35** (0.002 mole), sodium carbonate (0.002 mole) and ethanol (20 ml) was heated under reflux for 3h. The mixture was cooled, poured onto ice-water and neutralized with dilute hydrochloric acid. The precipitate was filtered off, washed with water, dried and recrystallized from ethanol to give **44**. Ir showed bands at 3525 -3450 cm^{-1} (OH),1663 cm^{-1} (CO).

4-Azido-2-methyl-3-nitroquinoline (45):

A mixture of **1** (0.5 g,0.002 mole), sodium azide (0.4g, 0.006 mole) and dimethylsulphoxide (10 ml) was stirred for 8 h. at room temperature. The reaction mixture was poured onto cold water and the precipitated product was filtered, washed with water to give **45.** Ir showed bands at 2080 cm^{-1}(N_3), 1555 cm^{-1} (NO2).

4-Methyl-3-oxo-1,2,5-oxadiazolo[3,4-c]quinoline (46):

a) The previous experiment was repeated but by heating at 90 ^{0}C for 6 hrs .The mixture was then poured onto cold water to give orange precipitate. The product was filtered, washed with water, dried and crystallized from benzene to give **46.**

b) Crystallization of the azide **45** from benzene afforded **46** which was identical with the product obtained by method (a). Ir showed bands at: 1555 cm^{-1} (NO). ^{1}H nmr spectra of compound **46** showed signals at: δ 8.5 (d,H8), δ 8.2 (m,H7), δ 7.8 (d,H5), δ 7.5 (m,H6), δ 2.6 ppm (s,CH_3).

4-(2-formylphenoxy)-2-Methyl-3-nitro-6- or 7-substitutedquinolines (47-50), 4-(2- carboxyphenoxy)-2-methyl-3-nitro-6- or 7-substitutedquinolines (51-54)

A mixture of **2-5** (0.00i94 mole), salycaldehyde or salicylic acid (3.62 mmole) and dry benzene (20 ml) was heated under reflux on a water-bath for 3h. The mixture was cooled, neutralized with sodium bicarbonate and the benzene layer was separated, washed with sodium bicarbonate solution, water and dried with anhydrous sodium carbonate. The solvent was evaporated and the residue was crystallized from ethanol. Ir **47-50** showed bands at:2810-1815 cm^{-1} (CHO), 1690-1680 cm^{-1} (CO), 1590-1550 cm^{-1}(NO2). **51-54:** 3450-3400 cm^{-1} (OH), 1650 -1630 cm^{-1} (CO), 1590 -1550 cm^{-1} (NO_2). Mass spectrum of **47:** m/z 342(2), 344(0.6), 300(3), 256(5), 225(5), 184(10), 149(20), 120(18), 98(70), 81(100). ^{1}H nmr **50:** δ 10.2 (CHO), δ 7.7-6.7 (m,7H,Ar), δ 3.0 (s,CH_3). **54:** δ (s,COOH), δ 7.5-6.7(m,7H,Ar.), δ 2.9 (s,CH_3), δ 2.3 ppm (s,CH_3).

2-Chloro-6-methyl-7-oxobenzopyrano[3,2-c]quinoline (55) or 2,6-dimethyl-7-oxo benzopyrano[3,2-c]quinoline (56): a) A mixture of **2** or **5** (0.00165 mole), salicylic acid or salicaldehyde (0.00362 mole), sodium carbonate (0.05 mole) and ethanol (10 ml) was heated under reflux for 4h. The mixture was filtered off. The filtrate was concentrated and cooled and the precipitate was collected and recrystallized from ethanol to give **55** and **56.**

A mixture of either **47** and **48** or **51** and **52** (1.65 mmole), sodium carbonate (0.05 mole) and ethanol (10 ml) was heated under reflux for 4h. The mixture was filtered off and the filtrate was concentrated and cooled. The precipitate was collected and recrystallized from ethanol to give **55** and **56.** Ir showed bands at 1680 cm^{-1}(CO).

Table 1: Mp. Yield and analytical data

Cpd. no	mp-	yield	formula (mol. Wt.)	analysis % calcd C	H	N	Cl	found C	H	N	Cl
11	214	59	$C_{10}H_{10}ClN_3$. (207.66)	57.83	4.85	20.23	17.07	57.41	4.7	20.3	17.3
12	232	29	$C_{10}H_{10}ClN_3$. (207.66)	57.83	4.85	20.23	17.07	57.6	4.8	20.3	17.2
13	146	20	$C_{11}H_{13}N_3$. (187.24)	70.55	6.99	22.44		70.5	7.1	22.5	
14	72	68	$C_{11}H_{13}N_3$. (187.24)	70.55	6.99	22.44		70.0	6.9	22.0	
15	249	54	$C_{12}H_{12}ClN_3$ (233.70)	61.66	5.17	17.98		61.4	5.2	18.1	
16	249	54	$C_{12}H_{12}ClN_3$ (233.70)	61.66	5.17	17.98		61.5	5.3	18.0	
17	229	17	$C_{13}H_{15}N_3$. (213.27)	73.2	7.08	19.7		73.4	6.9	19.4	
18	212	18	$C_{13}H_{15}N_3$. (213.27)	73.2	7.08	19.7		73.5	7.2	19.5	
19	227	18	$C_{12}H_{10}ClN_3$???. (231.68)	62.20	4.35	18.13		61.9	4.2	17.8	
20	223	17	$C_{12}H_{10}ClN_3$???. (231.68)	62.20	4.35	18.13		62.3	4.2	18.2	
21	227	51	$C_{13}H_{12}ClN_3O$ (261.71)	59.65	4.62	16.05		59.7	4.7	16.1	
22	198	15	$C_{13}H_{12}ClN_3O$ (261.71)	59.65	4.62	16.05		59.8	4.6	16.3	
23	202	17	$C_{14}H_{15}N_3O$ (241.28)	69.68	6.26	17.41		69.5	6.0	17.3	
24	202	17	$C_{14}H_{15}N_3O$ (241.28)	69.68	6.26	17.41		69.5	6.2	17.4	
25	112	67	$C_{17}H_{15}N_3O_2$ (293.31)	69.6	5.15	14.32		69.4	5.0	14.5	
26	159	78	$C_{17}H_{14}ClN_3O_2$.(327.76)	62.29	4.3	12.82		62.6	4.2	12.5	
27	157	78	$C_{17}H_{14}ClN_3O_2$.(327.76)	62.29	4.3	12.82		62.4	4.3	12.7	
28	159	77	$C_{18}H_{17}N_3O_2$. (307.34)	70..33	5.57	13.67		69.8	5.5	13.5	
29	130	61	$C_{18}H_{17}N_3O_2$. (307.34)	70..33	5.57	13.67		70.2	5.6	13.4	
30	262	79	$C_{17}H_{13}N_3O$ (275.30)	74.16	4.75	15.26		74.3	4.7	15.1	
31	243	76	$C_{17}H_{12}ClN_3O$.(309.75)	65.91	3.9	13.56	11.44	65.9	3.6	13.2	11.2
32	236	79	$C_{17}H_{12}ClN_3O$.(309.75)	65.91	3.90	13.56	11.44	65.8	3.8	13.4	11.3
33	238	79	$C_{18}H_{15}N_3O$. (289.32)	74.71	5.22	14.52		74.4	5.0	14.1	
34	221	80	$C_{18}H_{15}N_3O$. (289.32)	74.71	5.22	14.52		74.5	5.2	14.3	
35	206	55	$C_{12}H_{11}N_3O_4$ (261.23)	55.16	4.24	16.08		55.5	4.3	15.8	
36	134	36	$C_{12}H_{10}ClN_3O_4$.(295.68)	48.74	3.40	14.21				13.9	
37	136	40	$C_{12}H_{10}ClN_3O_4$.(295.68)	48.74	3.40	14.21		48.6	3.4	142	
38	130	25	$C_{13}H_{13}N_4O_4$. (289.27)	53.97	4.53	19.37		53.6	4.6	19.4	
39	150	75	$C_{21}H_{18}N_4O_4$. (390.39)	64.60	4.64	14.35		64.4	4.8	14.3	
40	200	67	$C_{15}H_{17}N_3O_4S$. (335.38)	53.71	5.10	12.53		53.5	4.9	12.8	
41	241	85	$C_{19}H_{17}N_3O_5$ (367.35)	62.11	4.66	11.43		61.9	4.6	11.1	
42	211	68	$C_{13}H_{13}N_3O_4$ (275.26)	56.72	4.76	15.26		56.6	4.9	14.9	
43	191	50	$C_{16}H_{19}N_3O_4$. (317.34)	60.55	6.03	13.24		60.9	5.9	12.9	
44	206	65	$C_{12}H_9N_3O_3$ (243.22)	59.25	3.73	17.27		59.5	3.9	17.4	
45	73	58	$C_{10}H_7N_5O_2$ (229.20)								
46	198	88	$C_{10}H_7N_3O$. (185.18)	64.85	3.81	22.69		64.5	3.6	22.7	
47	156	72	$C_{17}H_{11}ClN_2O_4$ (342.73)	59.57	3.23	8.17	10.34	59.6	3.1	7.8	9.9
48	190	72	$C_{17}H_{11}ClN_2O_4$ (342.73)	59.57	3.23	8.17	10.34	59.8	3.2	8..2	10.1
49	147	44	$C_{18}H_{14}N_2O_4$ (322.31)	67.07	4.37	8.69		67.3	4.4	8.5	
50	151	56	$C_{18}H_{14}N_2O_4$ (322.31)	67.07	4.37	8.69		67.2	4.3	8.6	
51	231	45	$C_{17}H_{11}ClN_2O_5$ (358.73)	56.91	3.09	7.80	9.88	56.6	3.2	8.2	9.5
52	230	40	$C_{17}H_{11}ClN_2O_5$ (358.73)	56.91	3.09	7.80	9.88	56.8	3.1	7.9	9.8
53	256	30	$C_{18}H_{14}N_2O_5$ (338.31)	63.90	3.09	7.80		63.8	3.1	7.6	
54	255	44	$C_{18}H_{14}N_2O_5$ (338.31)	63.90	3.09	7.80		63.7	2.9	7.7	
55	232	52	$C_{17}H_{10}ClNO_2$ (295.72)	69.04	3.4	4.73	11.99	69.1	3.7	4.7	11.9
56	157	46	$C_{18}H_{13}NO_2$ (275.29)	78.52	4.76	5.08		78.4	4.5	4.9	

References

[1] C. Philips, in: Malaria, Edward Arnold Ltd. London, PP 58 (1983).

[2] L. J. Bruce-Chwah, in: Chemotherapy of Malaria 2nd edn. World Health Organization, Geneva (1981)

[3] G. M. Bennet, P. C. Crofts,D. H. Hey, J. Chem. Soc., 227 (1949)

[4] A. Adams and D. H. Hey, J. Chem. Soc., 3185 (1949)

[5] G. Frauk, K. Rosemarie, Z. Felix, Arch. Pharm, **313**, 166 (1980)

[6] S. Fritz, J. Ulrich, R. Manfred, W. Josef, B. Carl; Ger. Offen. DE3,721,745 (1988); Chem. Abstr. **109**, 54790v (1988)

[7] H. Koga, A. Itoh and S. Murayama, J. Med. Chem. **23**, 1358 (1980)

[8] D. T. W. Chu, A. K. Claiborne, J. Heterocyclic Chem. **24**, 1537 (1987)

[9] R. Krishnor, S. A. Lang, M. M. Siegel, J. Heterocyclic Chem. **23**, 1801 (1986)

[10] D. B. Barnett, Lancet **341**, 733 (1993)

[11] R. E. Wieshaar, A. M. Walloce, L. A .Kisor, L. W. Britten, V. A. Ferraris, M. F. Sin, Br. J. Pharmacol. **107**, 105p (1991)

[12] D. B. Yates, Am. Heart J. **121**, 974 (1991)

[13] A. J. Cowley, R. D. Wynne and J. R. Hampton, J. Hypertens. **2**(3), 547 (1984)

[14] R. D. Wynne, E. L. Crampton, I. D. Hind, Eur. J. Clin.Pharm.**28**, 659 (1985)

[15] A. M. Brich, R. V. Davies, J Chem. Soc. Perkin Trans 1, 387 (1994)

[16] E. I. Ibrahim, A. M. Montgomerie, A. H. Sneddon, G. R. Proctor, B. Green, Eur.J.Med.Chem. **23**, 183 (1988)

[17] Y. Takeuchi; M. R. Chang; K. Hashigaki; T. Tashiro; S. Tsukagoshi;M. Yamato; Chem.Pharm.Bull.**40**, 528 (1992). Chem. Abstr.**117**, 48368 (1992)

[18] Takeda Chemical industries JPN, Kokai Tokkyo Koho 80, 111, 406 (1979), Chem. Abstr. **93**, 232704f.(1979)

[19] K. Ornfeld; C. Edmund; N. J. Bach, Belg.877,327 (1979). Chem. Abster. **93**, 71764h (1979)

[20] C. Coquelet; P. Hao Dong; M. Bastide; Eur. J. Med.. Chem. Chem. Ther. **15**, 119 (1980)

[21] M. P. Mayer; F. H. Weber; J. L. Gross, J. Med. Chem. **35**(24), 4595 (1992)

[22] J. S. Skotricki; B. A. Steinbaugh; J. Fitzgerald; R. M. Kearney; J. H. Musser; L. M. Adams; R. G. Caccese; J. Y. Chang; S. C. Jilman; Med. Chem. Res., **1**, 245 (1991); Chem. Abst.**117**, 184256b (1992)

[23] T. H. Brown; C. A. Leach; R. J. Ife; D. J. Keeling; Eur. Pat. 441,036 (1989); Chem. Abstr. **115**, 183306q (1991)

[24] H. Yongzhou; L. Kang;; W. Yijin; Z. Huijun; F. Ruiying; Zhejiang Yike Daxue Xuebao **20**, 251 (1991); Chem. Abstr. **117**, 90206h (19)

[25] F. Suzuki; T. Kuroda; Y. Nakasato; H. Manabe; K. Ohmori; S. Kitamura; S. Ichikawa, J. Med. Chem. **35**, 4045 (1992)

[26] N. A. Meanwell; R. D. Dennis; H. R. Roth; M. j. Rosenfeld; E. C. R. Smith; J. J. K. Wright; J. O. Buchanan; C. L. Brassad; M. Gamberdella, J. Med. Chem.**35**, 2688 (1992)

[27] M. Conrad; L. Limpach , Ber., **21**, 1981 (1888).

Received on September 18, 1999