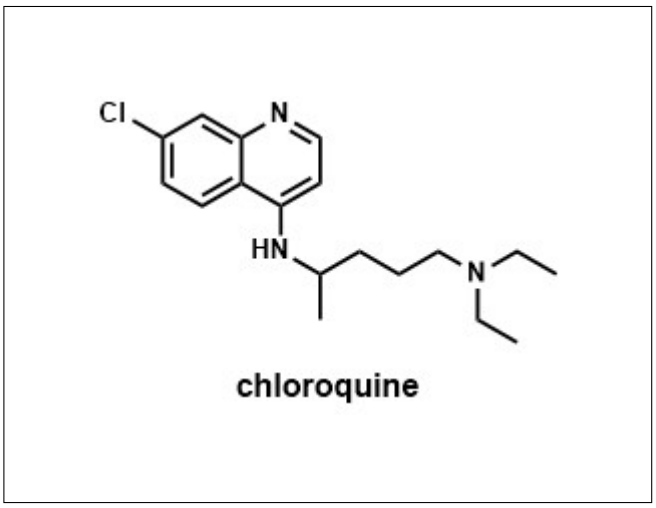
Chloroquine



Related reviews in Science of Synthesis

- Quinolines
- Quinolinamines
- Reductive Amination of Carbonyl Compounds

ATC: P01BA01
Use: antirheumatic, antimalarial
Chemical name: *N*4-(7-chloro-4-quinolinyl)-*N*1,*N*1-diethyl-1,4-pentanediamine
Formula: $C_{18}H_{26}ClN_3$
MW: 319.88 g/mol
CAS-RN:54-05-7
InChI Key: WHTVZRBIWZFKQO-UHFFFAOYSA-N
InChI: InChI=1S/C18H26ClN3/c1-4-22(5-2)12-6-7-14(3)21-17-10-11-20-18-13-15(19)8-9-16(17)18/h8-11,13-14H,4-7,12H2,1-3H3,(H,20,21)
EINECS: 200-191-2
LD_{50}: 21.6 mg/kg (M, i.v.); 311 mg/kg (M, p.o.); 60 mg/kg (R, i.v.); 330 mg/kg (R, p.o.)

Derivatives

diphosphate
Formula: $C_{18}H_{26}ClN_3 \cdot 2H_3PO_4$
MW: 515.87 g/mol
CAS-RN: 50-63-5
EINECS: 200-055-2
LD_{50}: 500 mg/kg (M, p .o.)

sulfate (1:1)
Formula: $C_{18}H_{26}ClN_3 \cdot H_2SO_4$
MW: 417.96 g/mol
CAS-RN: 132-73-0
EINECS: 205-077-6

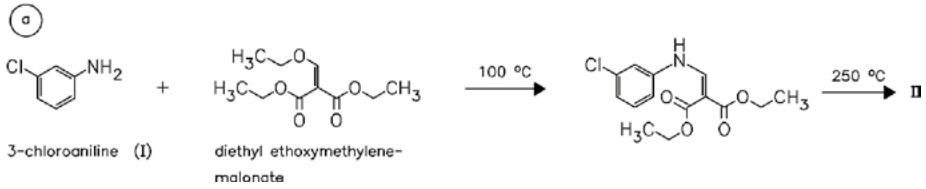
sulfate (1:1) monohydrate
Formula: $C_{18}H_{26}ClN_3 \cdot H_2O_4S \cdot H_2O$
MW: 435.97 g/mol
CAS-RN: 6823-83-2

dihydrochloride
Formula: $C_{18}H_{26}ClN_3 \cdot 2HCl$
MW: 392.80 g/mol
CAS-RN: 3545-67-3
EINECS: 222-592-1

2,5-dihydroxybenzoate
Formula: $C_{18}H_{26}ClN_3 \cdot xC_7H_6O_4$
MW: unspecified
CAS-RN: 16510-14-8
EINECS: 240-578-3

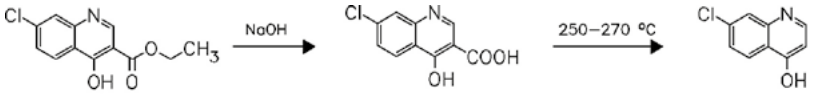
diorotate
Formula: $C_{18}H_{26}ClN_3 \cdot 2C_5H_4N_2O_4$
MW: 632.07 g/mol
CAS-RN: 16301-30-7
EINECS: 240-389-6
LD_{50}: 1130 mg/kg (M, p.o.)

starting products:
1. 4.7-Dichloroquinoline



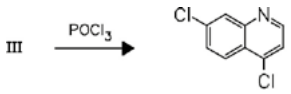
3-chloroaniline (I)

diethyl ethoxymethylene-malonate

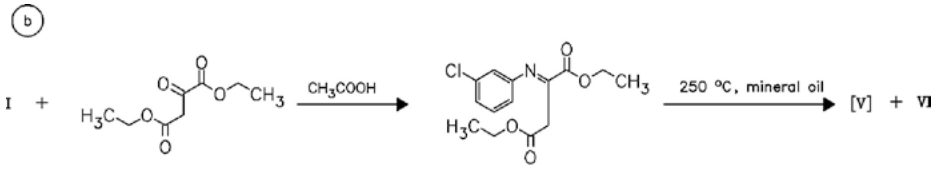


ethyl 7-chloro-4-hydroxy-3-quinoline-carboxylate (II)

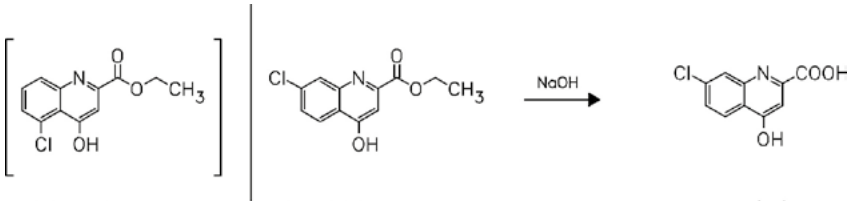
7-chloro-4-hydroxy-quinoline (III)



4,7-dichloro-quinoline (IV)



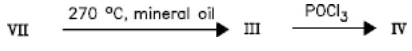
diethyl oxaloacetate



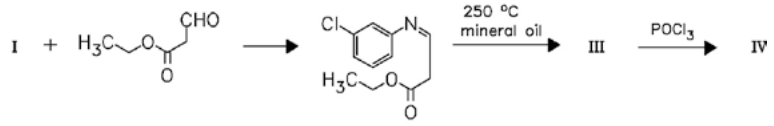
ethyl 5-chloro-4-hydroxy-2-quinoline-carboxylate (V) (removal by crystallization from acetic acid)

ethyl 7-chloro-4-hydroxy-2-quinoline-carboxylate (VI)

(VII)



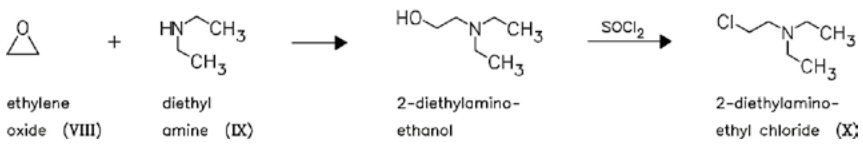
c



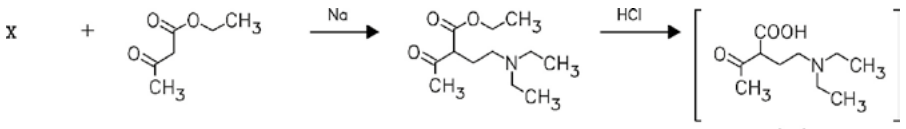
ethyl formyl-
acetate

2. Novoldiamine

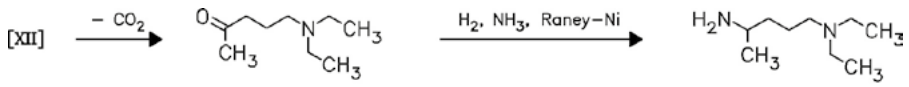
a



ethylene oxide (VIII) | diethyl amine (IX) | 2-diethylamino-ethanol | 2-diethylamino-ethyl chloride (X)

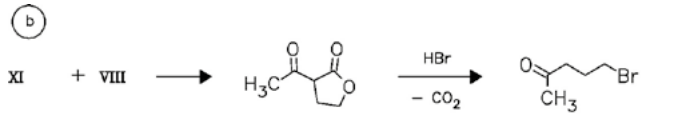


ethyl acetoacetate (XI) | (XII)

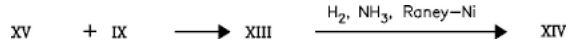


1-diethylamino-4-pentanone (XIII) | novoldiamine (XIV)

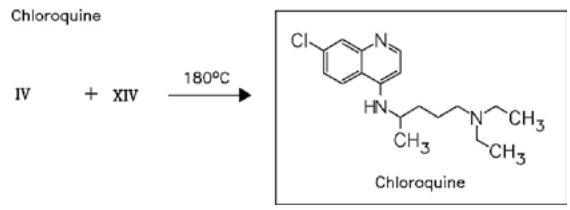
b



2-acetyl-butyrolactone | 1-bromo-4-pentanone (XV)



final product:
Chloroquine



Substances Referenced in Synthesis Path

CAS-RN	Formula	Chemical Name	CAS Index Name
141-97-9	$C_6H_{10}O_3$	acetoacetic acid ethyl ester	Butanoic acid, 3-oxo-, ethyl ester
517-23-7	$C_6H_8O_3$	2-acetylbutyrolactone	2(3H)-Furanone, 3-acetyldihydro-
140-80-7	$C_9H_{22}N_2$	2-amino-5-diethylaminopentane	1,4-Pentanediamine, N1,N1-diethyl-
3884-71-7	C_5H_9BrO	1-bromo-4-pentanone	2-Pentanone, 5-bromo-
108-42-9	C_6H_6ClN	3-chloroaniline	Benzenamine, 3-chloro-
86-99-7	C_9H_6ClNO	7-chloro-4-hydroxyquinoline	4-Quinolinol, 7-chloro-
18000-24-3	$C_{10}H_6ClNO_3$	7-chloro-4-hydroxy-2-quinolinecarboxylic acid	2-Quinolinecarboxylic acid, 7-chloro-4-hydroxy-
86-47-5	$C_{10}H_6ClNO_3$	7-chloro-4-hydroxy-3-quinolinecarboxylic acid	3-Quinolinecarboxylic acid, 7-chloro-4-hydroxy-
3412-99-5	$C_{14}H_{16}ClNO_4$	[[(3-chlorophenyl)amino]methylene]propanedioic acid diethyl ester	Propanedioic acid, [[(3-chlorophenyl)amino]methylene]-, diethyl ester
	$C_{14}H_{16}ClNO_4$	α-[(2-chlorophenyl)imino]butanedioic acid diethyl ester	
82673-23-2	$C_{11}H_{12}ClNO_2$	3-[(3-chlorophenyl)imino]propanoic acid ethyl ester	
86-98-6	$C_9H_5Cl_2N$	4,7-dichloroquinoline	Quinoline, 4,7-dichloro-
109-89-7	$C_4H_{11}N$	diethylamine	Ethanamine, N-ethyl-
100-35-6	$C_6H_{14}ClN$	2-diethylaminoethyl chloride	Ethanamine, 2-chloro-N,N-diethyl-
105-14-6	$C_9H_{19}NO$	1-diethylamino-4-pentanone	2-Pentanone, 5-(diethylamino)-
87-13-8	$C_{10}H_{16}O_5$	diethyl ethoxymethylenemalonate	Propanedioic acid, (ethoxymethylene)-, diethyl ester
108-56-5	$C_8H_{12}O_5$	diethyl oxaloacetate	Butanedioic acid, oxo-, diethyl ester
108-01-0	$C_4H_{11}NO$	2-dimethylaminoethanol	Ethanol, 2-(dimethylamino)-
87-13-8	$C_{10}H_{16}O_5$	ethoxymethylenemalonic acid diethyl ester	Propanedioic acid, (ethoxymethylene)-, diethyl ester
141-97-9	$C_6H_{10}O_3$	ethyl acetoacetate	Butanoic acid, 3-oxo-, ethyl ester
21640-98-2	$C_{12}H_{10}ClNO_3$	ethyl 5-chloro-4-hydroxy-2-quinolinecarboxylate	2-Quinolinecarboxylic acid, 5-chloro-4-hydroxy-, ethyl ester
21640-97-1	$C_{12}H_{10}ClNO_3$	ethyl 7-chloro-4-hydroxy-2-quinolinecarboxylate	2-Quinolinecarboxylic acid, 7-chloro-4-hydroxy-, ethyl ester
16600-22-9	$C_{12}H_{10}ClNO_3$	ethyl 7-chloro-4-hydroxy-3-quinolinecarboxylate	3-Quinolinecarboxylic acid, 7-chloro-4-hydroxy-, ethyl ester
23999-02-2	$C_{12}H_{23}NO_3$	ethyl 2-(2-diethylaminoethyl)acetoacetate	Butanoic acid, 2-[2-(diethylamino)ethyl]-3-oxo-, ethyl ester
75-21-8	C_2H_4O	ethylene oxide	Oxirane
34780-29-5	$C_5H_8O_3$	ethyl formylacetate	Propanoic acid, 3-oxo-, ethyl ester
140-80-7	$C_9H_{22}N_2$	novoldiamine	1,4-Pentanediamine, N1,N1-diethyl-

Trade Names

Country	Trade Name	Vendor	Annotation
D	Resochin	Bayer Vital	
F	Nivaquine	Sanofi-Aventis	
	Savarine	AstraZeneca	
GB	Avloclor	AstraZeneca	
I	Clorochina	Formulario NazionaleBayer	
USA	Aralen	Sanofi	as hydrochloride
	Aralen	Sanofi	as phosphate

Formulations

amp. 250 mg/5 ml; syrup 15 mg; tabl. 50 mg, 155 mg, 300 mg (as phosphate)

References

Drake, N.L. et al.: J. Am. Chem. Soc. (JACSAT) 68, 1214 (1946).
1 a Price, C.C.; Roberts, R.M.: J. Am. Chem. Soc. (JACSAT) 68, 1204 (1946).
b Surrey, A.R.; Hammer, H.F.: J. Am. Chem. Soc. (JACSAT) 68, 113 (1946).
2 b Elderfield, R.C. et al.: J. Am. Chem. Soc. (JACSAT) 68, 1579 (1946).
US 2 233 970 (Winthrop; 1941; D-prior. 1937).
DRP 683 692 (I. G. Farben; appl. 1937).
DD 53 065 (S. Schwarz et al.; appl. 1966).
c US 2 478 125 (American Cyanamid; 1949; appl. 1944).
2 a DRP 486 079 (I. G. Farben; appl. 1924).

***alternative syntheses of* novoldiamine:**
US 2 365 825 (Monsanto; 1944; appl. 1942).
GB 1 157 637 (Sterling Drug; appl. 1966; USA-prior. 1965).

aminating hydrogenation of* novolketone, *continuous method:
DOS 2 923 472 (Bayer; appl. 9.6.1979).

alternative synthesis of* 4,7-dichloroquinoline *from* 3-chloroaniline *and acrylic acid ester:
FR 1 514 280 (Roussel-Uclaf; appl. 10.1.1967).
EP 56 765 (Rhône-Poulenc; appl. 15.1.1982; F-prior. 16.1.1981).

***alternative synthesis of* chloroquine *from* 7-chloro-4-oxo-1,2,3,4-tetrahydroquinoline *and* novoldiamine:**
EP 56 766 (Rhône-Poulenc; appl. 15.1.1982; F-prior. 16.1.1981).

***chlorination of* 7-chloro-4-hydroxyquinoline *with* benzotrichloride:**
DOS 3 112 415 (Dynamit Nobel; appl. 28.3.1981).