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Synthesis of 1-(Aminoalkylamino)-3,4-Dimethoxynaphthalenes As Antimalarial Agents with Radical Curative Activity

Annual and Final Report

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1-(4'-Amino-1'-methylbutylamino)-7-bromo-3,4-dimethoxynaphthalene;
1-(4'-Amino-1'-methylbutylamino)-7-chloro-3,4-dimethoxynaphthalene;
1-(4'-Amino-4'-methylbutylamino)-7-chloro-3,4-dimethoxynaphthalene;
1-(4'-Amino-1'-methylbutylamino)-6-chloro-3,4-dimethoxynaphthalene.

20. ABSTRACT (Continue on reverse side if necessary and identify by block number)

The 1-(Aminopentylamino)-7 and 6-halo-3,4-dimethoxynaphthalenes were prepared by condensing the appropriate halopentylphthalimides with the requisite 1-Amino-6 or 7-halo-3,4-dimethoxynaphthalenes and removing the protective group with hydrazine. The four target compounds were obtained as analytically pure crystalline fumarate salts.

Amino compounds, naphthalenes, chlorine compounds, pentyl radicals, synthesis (chemistry).

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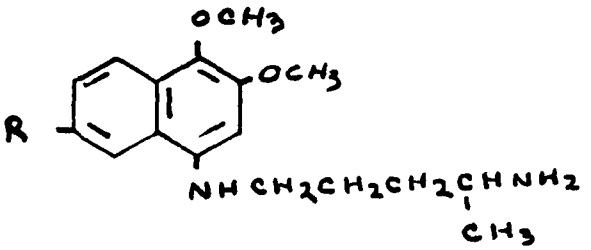
ABSTRACT

Four target compounds were prepared as potential radical curative agents in malaria 1-(4'-amino-1'-methylbutylamino)-7-bromo,3,4-dimethoxynaphthalene and 1-(4'-amino-1'-methyl butylamino)-7-chloro-3,4-dimethoxynaphthalene were prepared by condensing N(4-bromopentyl)phthalimide with 1-amino-7-bromo-3,4-dimethoxynpahthalene and 1-amino-7-chloro-3,4-dimethoxynapthalene respectively, and converting the condensation products to their respective primary amines with the aid of hydrazine. Condensation of the same bromopentylphthaliamide with 1-amino-6-chloro-3,4-dimethoxynaphthalene followed by hydrazinolysis gave 1-(4'-amino-1'-methylbutylamino-6-chloro-3,4-dimethoxynapahthalene. Condensation of N-(4-iodo-2-pentylphthalimide with 1-amino-7-chloro-3,4-dimethoxynpahthalene followed by hydrazinolysis of the reaction product gave 1-(4'-amino-4'-methylbutylamino)-7-chloro-3,4-dimethoxynaphthalene.

Preface. Contract No. DAMD 17-80-C-0112 was awarded on 1 August 1980 originally for a period of three years to be renewed annually. However, at the end of the second year, the P.I. was informed by his contract monitor that this contract would be terminated at the end of the second year on 31 August 1982. A no cost extension was granted until 31 December 1982.

Introduction. In 1974 the Principal Investigator was awarded a contract by WRAIR (DAMD 17-74-C-4099) to prepare a series of 1-(aminoalkylamino)-3,4-dimethoxynaphthalenes as potential antimalarial agents with radical curative activity. About 3 of 6 of the target molecules showed curative action in cynomolgus infected monkeys. Of particular interest were the observations that while I (R=H) was inactive at 1.0 mg/kg but toxic at 10.0 mg/kg, II (R=Br) was inactive at 1.0 mg/kg but was curative 10.0 mg/kg.



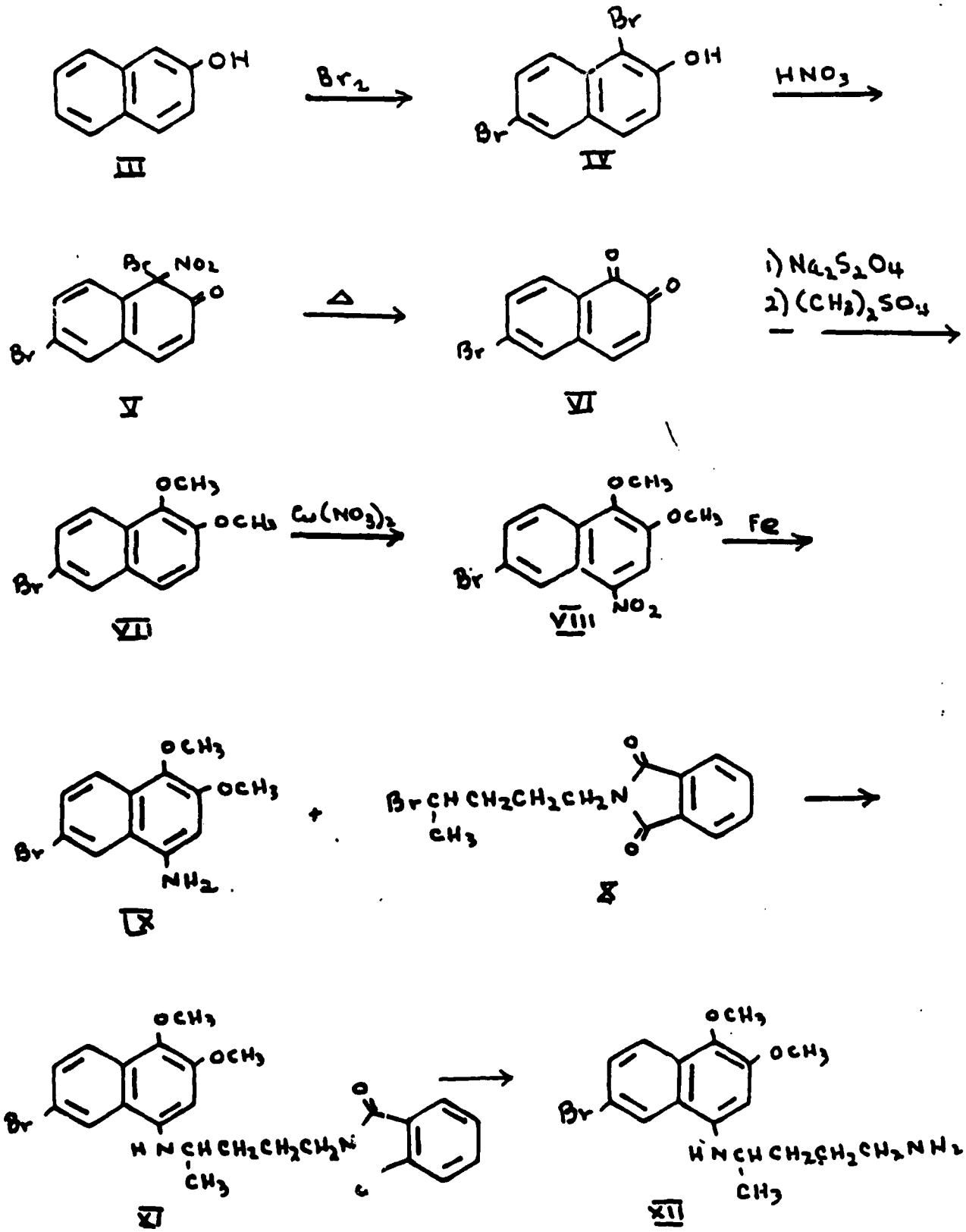
I, R=H

II, R=Br

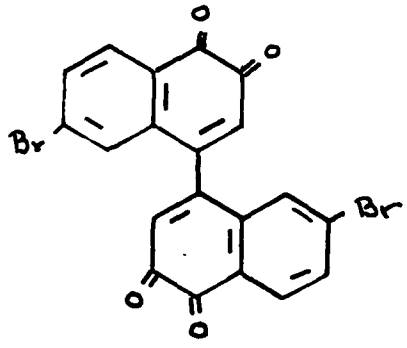
Therefore we decided to prepare congeners of II as potential antimalarial agents with radical curative activity.

Chemistry. Target compound XII was prepared as shown in Scheme I.

Scheme 1


OH
Br2
Br
OH
Br
HNO3
III
IV
Br
NO2
O
Br
Δ
O
O
Br
1) Na2S2O4
2) (CH3)2SO4
V
VI
OCH3
OCH3
Br
Cu(NO3)2
OCH3
OCH3
Br
Fe
NO2
VII
VIII
OCH3
OCH3
Br
NH2
IX
+
Br CH CH2CH2CH2N
CH3
O
O
X
OCH3
OCH3
Br
H N CH CH2CH2CH2N
CH3
O
Cl
XI
OCH3
OCH3
Br
H N CH CH2CH2CH2NH2
CH3
XII

β-Naphthol (III) was brominated to give 1,6-dibromonaphthol IV. Nitration gave the dibromo-nitro ketone V which on careful heating decomposed to give the 6-bromo-1,2-naphthoquinone VI. Reduction with sodium hydrosulfite gave the air-sensitive 6-bromo-1,2-naphthalene-diol which was not isolated but methylated to give 6-bromo-1,2-dimethoxynaphthalene VII. Nitration with cupric nitrate gave the desired 6-bromo-1,2-dimethoxy-4-nitronaphthalene VIII instead of a dimeric 1,2-naphthoquinone XIII which would have resulted had

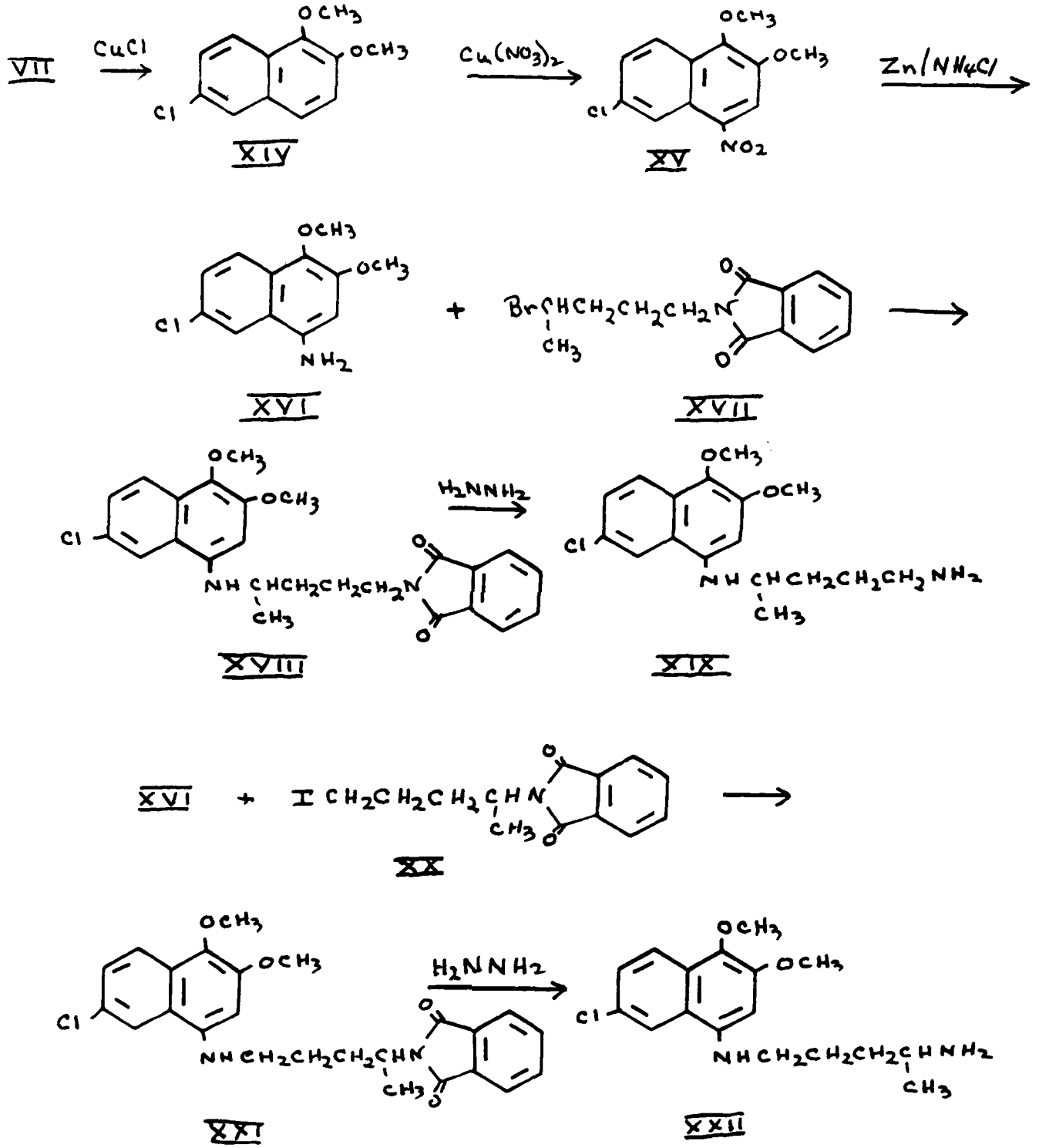


XIII

HNO_3 been used as the nitrating agent. Reduction with iron gave IX. This condensed with the bromopentylphthalimide (X) (obtained through the courtesy of Dr. H. A. Musallam) to give XI. The phthalimide (XI) was treated with hydrazine to liberate the target compound, XII, which was isolated as the fumarate salt.

The synthesis of the 4-(aminoalkylamino)-7-chloro-3,4-dimethoxy-naphthalenes (XXIV) and (XXVII) were carried out as shown in Scheme 2.

Scheme 2


VII
CuCl
OCH3
OCH3
Cl
XIV
Cu(NO3)2
OCH3
OCH3
Cl
NO2
XV
Zn/NH4Cl
OCH3
OCH3
Cl
NH2
XVI
+
Br
CHCH2CH2CH2N
CH3
O
O
XVII
H2NNH2
XVIII
XIX
XVI
+
I
CH2CH2CH2CHN
CH3
O
O
XX
H2NNH2
NHCH2CH2CH2CHN
CH3
XXI
NHCH2CH2CH2CHNH2
CH3
XXII

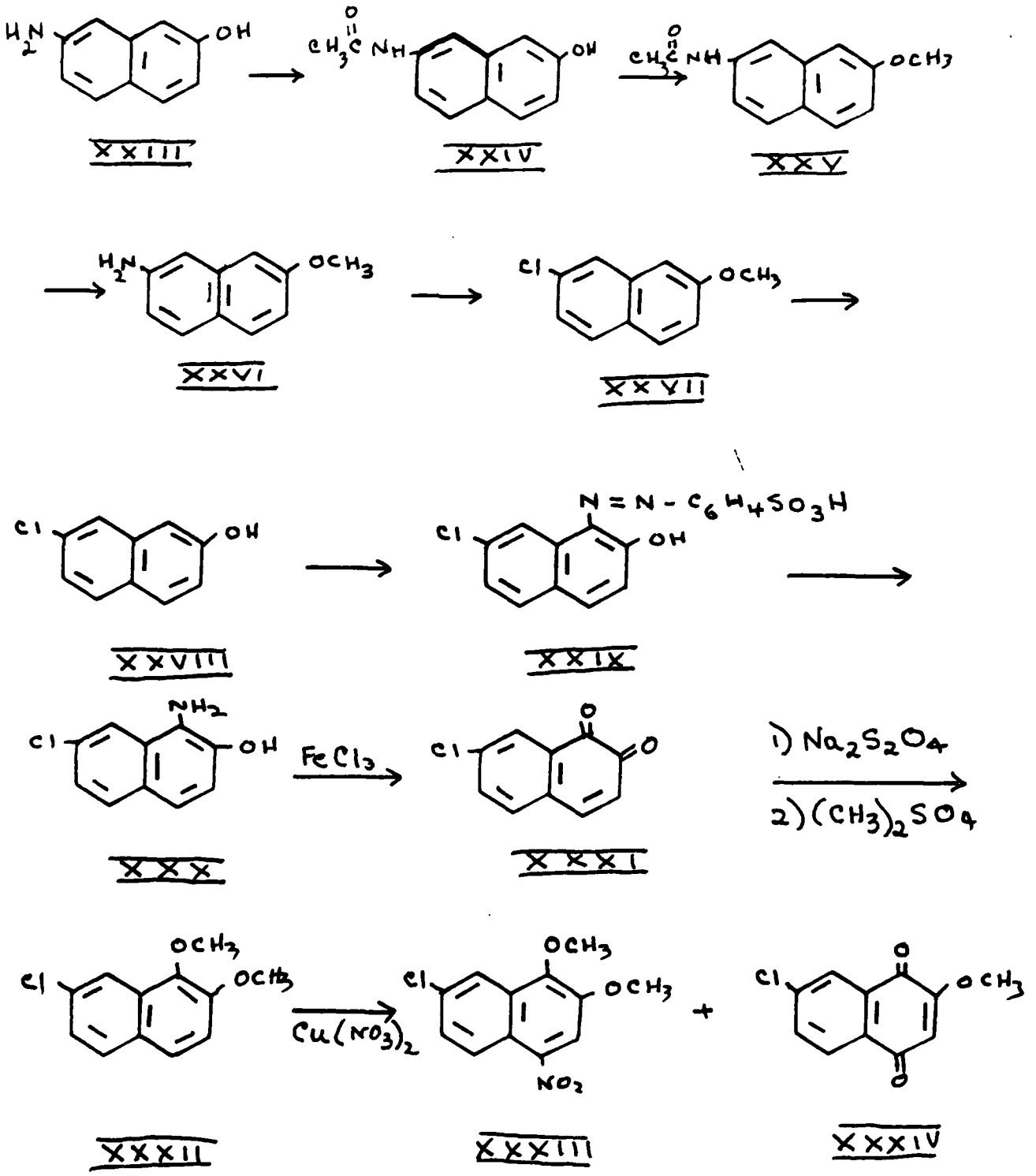
Treatment of VII with CuCl gave XIV nitration of which gave XV. Reduction to XVI was best carried out with Zn/NH_4Cl. Coupling with the bromoalkylphthalimide XVII gave XVIII which on hydrazinolysis gave XIX isolated as the crystalline fumarate salt.

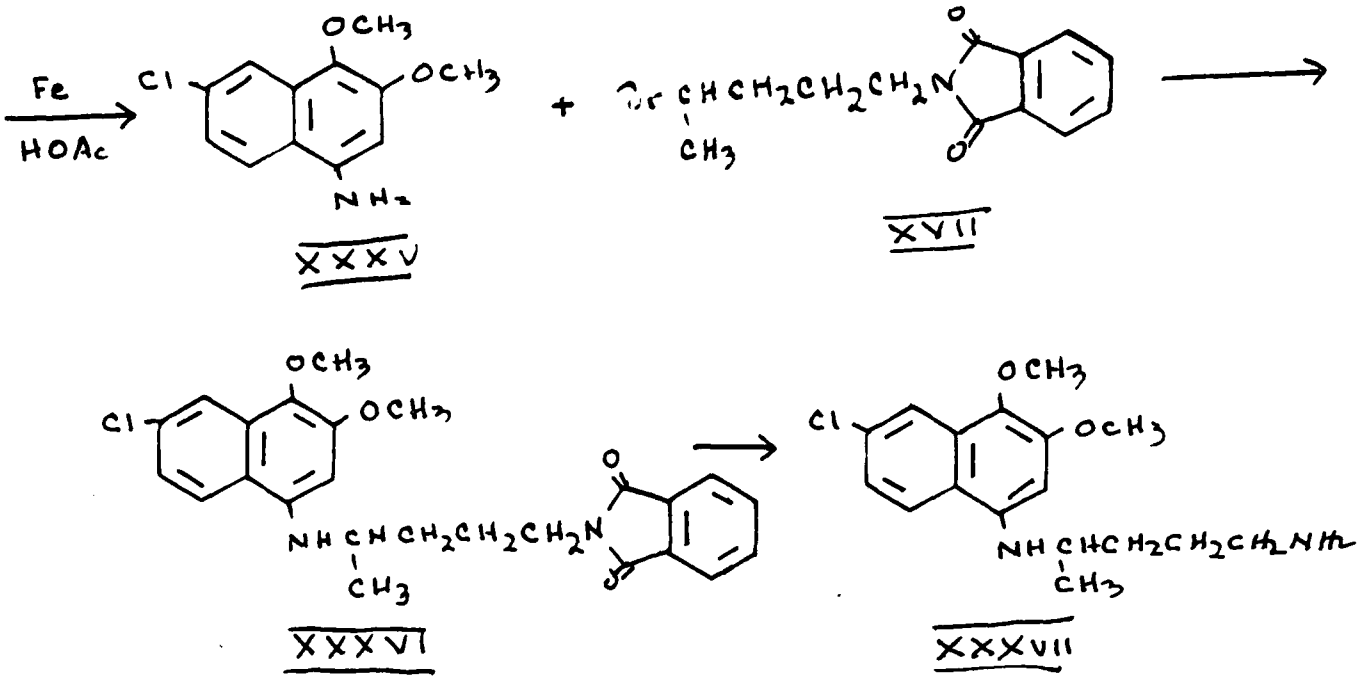
Condensation of XVI with the iodoalkylphthalimide XX gave XXI which was converted to XXII, isolated as the fumarate salt.

Thus we succeeded in preparing two 1-aminoakylamino-6-chloro-3,4-dimethoxy naphthalene derivatives. The preparation of an isomeric 7-chloro derivative was carried out as shown in Scheme 3.

7-Amino-2-naphthol (XXIII) was acetylated to give XXIV which was converted to the methyl ether XXV and then hydrolysed to give the free amino compound XXVI. A Sandmeyer reaction gve XXVII, demethylation of which with conc. HBr gave 7-chloro-2-naphthol (XXVIII). Treatment with diazotized sulfanilic acid gave the azo derivative XXIX which on reduction furnished the aminonaphthol XXX. Oxidation with $FeCl_3$ gave the 1,2-naphthoquinone XXXI which after reductive methylation gave XXXII. Nitration with $Cu(NO_3)_2$ in acetic anhydride at low temperature gave the desired nitro compound, XXXIII, accompanied by an almost equal amount of 7-chloro-2-methoxy-1,4-naphthoquinone XXXIV. Reduction of XXXIII with Fe in acetic acid gave the desired amino derivative XXXV which was condensed with XVII to give XXXVI. Hydrazinolysis furnished the desired target compound XXXVII isolated as a crystalline fumarate salt.

Scheme 3


XXIII
XXIV
XXV
XXVI
XXVII
XXVIII
XXIX
XXX
XXXI
XXXII
XXXIII
XXXIV
FeCl3
1) Na2S2O4
2) (CH3)2SO4
Cu(NO3)2



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