CHAPTER IV

RESULTS AND DISCUSSIONS

In this research, pyrazoloquinolones were synthesized. The 4-chloroquinoline-3-carboxylates intermediates were prepared as the modified Gould - Jacobs cyclization, and follow by thionyl chloride. The synthesis of 2-arylpyrazoloquinolones which are readily obtained from heating 4-chloroquinoline -3-carboxylate with phenylhydrazine in xylene. Treatment of the hydrazine with 4-chloroquinoline -3-carboxylates with sodium ethoxide in aqueous ethanol at room temperature yield the 2H-pyrazolo quinolones smoothly.

5-Ethyl-2-arylpyrazolo [4,3-c] quinolin-3-one (8a)

8a was selected as a model for studying the preparation of desired product. Various individual steps in the overall synthesis of 5-ethyl-2-arylpyrazolo [4, 3-c] quinolin-3-one are discussed as following.
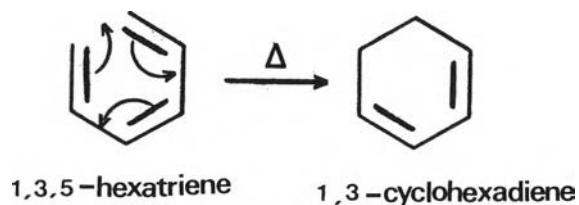
a)   3-Carboethoxy-4-hydroxyquinoline (5a)

5a was synthesized following the method of Gould and Jacob (1939) which contained two steps. The first step involves a condensation reaction between aniline and diethyl ethoxymethylenemalonate to yield ethyl anilinomethylenemalonate, which subject to further reaction without purification. Mechanistically, this process results from a nucleophilic attack of aniline upon the diethyl ethoxymethylenemalonate. The ethoxy group is expelled to form ethanol and the corresponding ethyl anilinomethylenemalonate was obtained shown as following.
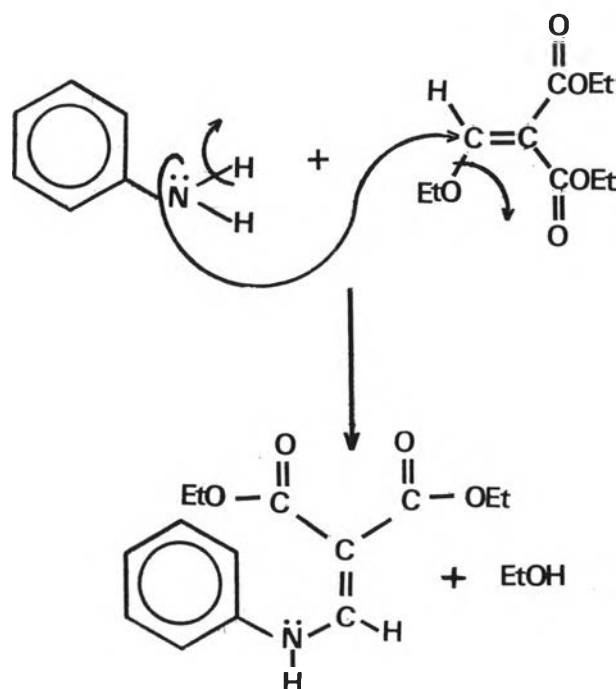

The IR spectrum of ethyl anilinomethylene-malonate (4a) (Figure 4) showed a strong C=O stretching

absorption peak at 1730 cm^{-1}, a peak between 1200 - 1290 cm^{-1} for C-O stretching vibration, a peak at 1618 cm^{-1} for N-H bending vibration and the C-H stretching vibration showed in the region 2850 - 3030 cm^{-1}. The ^{1}H-NMR spectrum of 4a (Figure 5) showed the peak at chemical shift 1.21 ppm (multiplet, 6H) for two methyl protons, the peak at 4.11 ppm (multiplet, 4H) for two methylene protons adjacent to oxygen ester. The peak at 7.14 - 7.32 ppm (multiplet, 5H) represented aromatic protons, the peak at 8.37 ppm (doublet, 1H) for methine proton adjacent to amino group and peak of secondary amine proton showed at chemical shift 10.69 ppm (doublet, 1H).

The second stage of reaction is the cyclization of ethyl anilinomethylenemalonate at high temperature. Heating the compound in high - boiling solvents, diphenyl ether afford the cyclization smoothly. The cyclization step may be rationalized as an orbital symmetry - allowed electrocyclic reaction. Enolization of ethyl anilinomethylenemalonate give XXXXI, which can be considered as analogues to 1, 3, 5-hexatriene. Such trienes are known to cyclize thermally to 1, 3-cyclohexadienes, and a corresponding reaction with XXXXI would give intermediate (XXXXII).

1,3,5-hexatriene   1,3-cyclohexadiene

The intermediate (XXXXII) loses ethanol and completes the conversion of ethyl anilinomethylenemalonate to 3-carboethoxy 4-hydroxyquinoline. Although cyclizations of 1, 3, 5-hexatriene normally occur at temperature required to produce 3-carboethoxy -4- hydroxyquinoline presumably reflects the loss of aromaticity associated with the formation of intermediate (XXXXXII) from XXXXI.
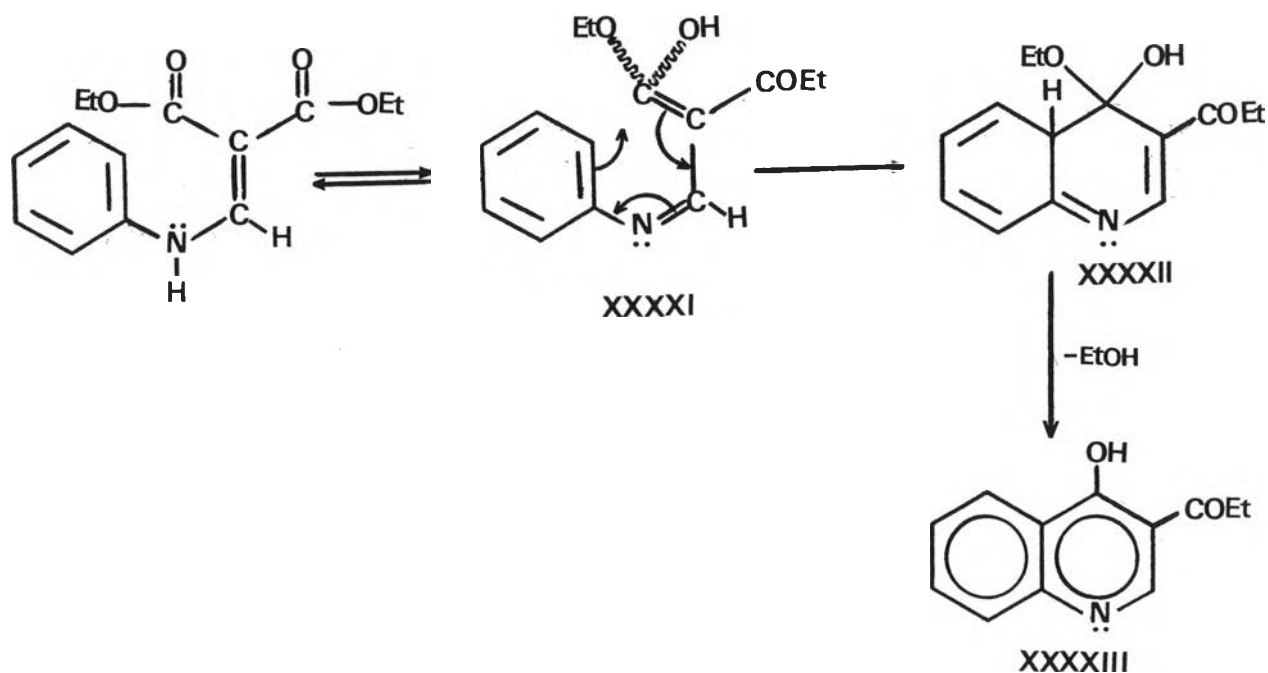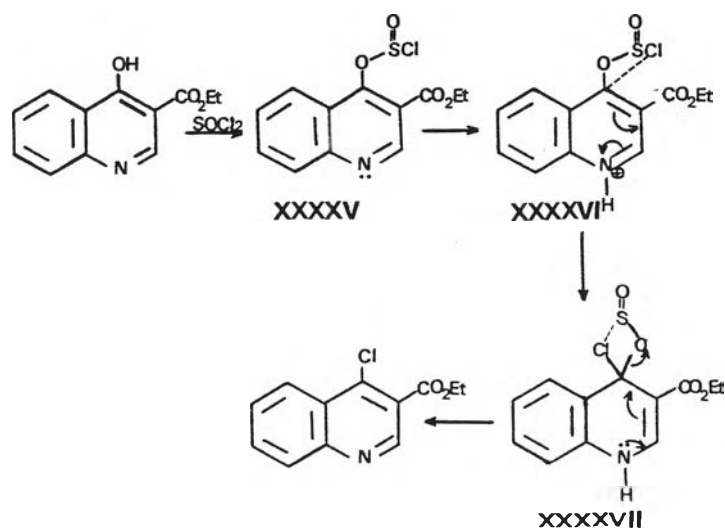
The IR spectrum of 3-carboethoxy-4-hydroxy quinoline (5a) (Figure 8) showed C-H stretching vibration in the region 2890 - 3150 cm^{-1}, a strong peak at 1700 cm^{-1} for C=O stretching absorption of ester, peak at 1198 and 1287 cm^{-1} for the C-O stretching vibration. In addition, the C=N stretching vibration was found at peak 1620 cm^{-1}, the O-H bending at peak 1380 cm^{-1}. The ^{1}H-NMR of 3-carboethoxy -4-hydroxyquinoline (5a) (Figure 9) showed the peak at chemical shift 1.28 ppm (triplet, 3H) for methyl protons, the peak at 4.21 (quartet, 2H) for methylene protons adjacent oxygen ester. The peak at 7.41 ppm (triplet, 1H) represented aromatic proton para nitrogen atom, the peak between chemical shift 7.59 - 7.75 ppm (multiplet, 2H) for two aromatic protons meta and ortho to nitrogen atom, the peak at 8.15 ppm (doublet, 1H) for aromatic proton ortho to pyridine fused the peak at 8.56 ppm (singlet, 1H) for aromatic proton adjacent nitrogen atom in pyridine ring, and the broad peak of hydroxy proton at 12.3 ppm (broad, 1H).

b) <u>3-Carboethoxy-4-chloroquinoline</u> (6a)

This step is the chlorination of 3-carboethoxy-4-hydroxyquinoline with thionyl chloride. The

phenolic hydroxyl group was replaced with chlorine atom to produce 3-carboethoxy-4-chloroquinoline. The 3-carbo ethoxy-4-hydroxyquinoline thus obtained was treated with excess thionyl chloride. This synthetic procedure was allowed according to method by Kaslow and Clark (1953) which the phosphorus trichloride was used as a source of chloride ion.

A possible mechanism for this transformation involves initial attack of the hydroxyl group of 3-carboethoxy -4-hydroxyquinoline on the thionyl chloride give intermediate (XXXXV) and hydrogen chloride which combine to give the salt (XXXXVI). This intermediate then undergoes nucleophilic aromatic substitution by chlorine atom, a process that is facilitated by the presence of the positive charge nitrogen atom which becomes neutralized upon addition of chloride to the ring (XXXXVII) as following.

XXXXV   XXXXVI

XXXXVII

The IR spectrum of 3-carboethoxy -4-chloroquinoline (6a) (Figure 12) showed C-H stretching vibrations in the region 2930 - 3070 cm^{-1}, strong peak at 1734 cm^{-1} for C=O stretching vibration of ester, peak at 1172 cm^{-1} and 1232 cm^{-1} for C-O stretching vibration, peak at 1582 cm^{-1} for C=C stretching vibration and peak at 1485 cm^{-1} for C-H bending vibration (CH$_2$CH$_3$). The ^{1}H-NMR spectrum of 6a (Figure 13) showed the peak at 1.43 ppm (triplet, 3H) for methyl protons, the peak at 4.47 ppm (quartet, 2H) for methylene protons adjacent oxygen ester, the peak at 7.66 ppm (triplet, 1H) for aromatic proton para to nitrogen atom, the peak at 7.80 ppm (triplet, 1H) for aromatic proton meta to nitrogen atom, the peak at 8.10 ppm (doublet, 1H) for proton ortho to fused pyridine ring and meta to nitrogen atom the peak at 8.36 ppm (doublet, 1H) for proton ortho to pyridine nitrogen and the peak at 9.17 ppm (singlet, 1H) for aromatic proton adjacent to nitrogen atom in pyridine ring.
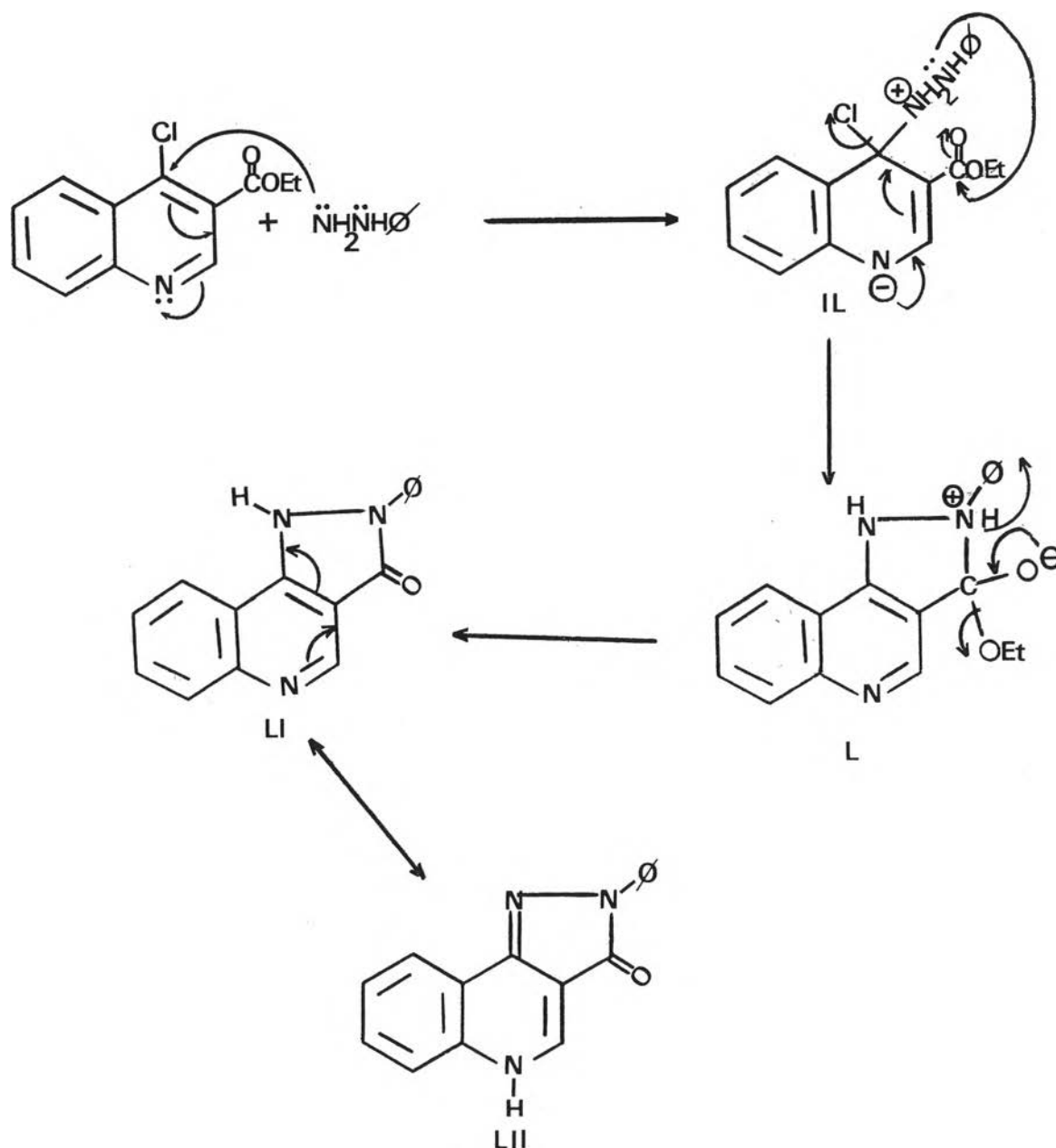
c) 2-Arylpyrazolo [4, 3-c] quinolin -3-one (7a)

The synthesis of 7a was readily accomplished by heating a mixture of 3-carboethoxy -4-chloroquinoline with phenylhydrazine at 130-150°C in xylene. The

separation of 2-arylpyrazoloquinolin -3-one from xylene was accomplished by extracting with aqueous sodium hydroxide. Upon acidified the aqueous basic solution acidic liberates the 2-aryl pyrazoloquinolin -3-one was liberated precipitates from solution. Since phenylhydrazine is a weak base and therefore is a weaker nucleophile, either high temperature or catalyst was required to promote the cyclization reaction to give a pyrazolo moiety directly.

The reaction involved nucleophilic aromatic substitution, with phenylhydrazine serving as the nucleophile. Initial, attack of amino group in phenylhydrazine on 3-carboethoxy-4-chloroquinoline to give intermediate precursor (IL), a process that is facilitated by positively charged nitrogen atom give phenylhydrazine intermediate and hydrogen chloride which serves by excess phenylhydrazine then, the carbonyl carbon of ester was attacked by the second nitrogen lone pair electrons to give 2-aryl pyrazoloquinolin-3-one intermediate (L). The intermediate (L) lost ethanol and converted as 2-arylpyrazolo quinolin-3-one (LI) which could be tautomerized give (LII). As possible, the both processes of cyclized spontaneously and attacking of phenylhydrazine

nucleophile on 3-carboethoxy -4-chloroquinoline were
formed almost altogether, with the phenylhydrazine
intermediate could not be isolated under this reaction
condition.

The IR spectrum of 2-arylpyrazolo [4,3-c]
quinolin 3-one (7a) (Figure 16) showed C-H stretching
vibration in the region 2880 - 2950 cm^{-1}, strong peak at

1627 cm^{-1} for C=O stretching vibration of amide, the peak at 1588 cm^{-1} represented C=C stretching vibration and the peak at 1300 cm^{-1} for C-N stretching vibrations of amide. The ^{1}H-NMR of 7a (Figure 17) showed the peak at 7.17 ppm (triplet, 1H) for phenyl proton at position para to nitrogen amide (N-2), the peak at 7.35 (triplet, 2H) for two phenyl protons at meta to nitrogen amide. The peak at 7.42 - 7.60 ppm (multiplet, 3H) represented three aromatic protons (in benzene system) at para and meta to pyridine nitrogen, the peak at 8.17 ppm (doublet, 2H) for two phenyl protons ortho to nitrogen amide, the peak at 8.22 ppm (doublet, 1H) for aromatic proton (in benzene system) ortho to pyridine nitrogen, the peak at 8.37 ppm. (doublet, 1H) for proton adjacent nitrogen in pyridine system and broad peak at 12.46 ppm (broad, 1H) for N-H proton. However, the different of ^{1}H-NMR spectrum of this same product when DMSO-d_6 with $CDCl_3$ was used as solvent (Figure 18) showed peak at 7.18 ppm (triplet, 1H) for phenyl proton para to nitrogen amide (N-2), the peak at 7.43 ppm (triplet, 2H) for two phenyl protons meta to nitrogen amide, the peak at 7.58 - 7.77 ppm (multiplet, 3H) for aromatic protons in benzene system at position meta (two protons) and para (one proton) to pyridine

nitrogen the peak at 8.21 ppm (doublet, 3H) represented two phenyl proton ortho to nitrogen amide (N-2) and aromatic proton ortho to pyridine nitrogen, the peak of N-H proton at 12.84 ppm (broad, 1H). For most different, chemical shift of proton adjacent to nitrogen in pyridine ring appeared at the lower field moreover, not found characteristic of coupling with nitrogen proton adjacent. It may caused by tautomeric structure of 2-arylpyrazolo [4,3-c] quinolin -3-one which showed its proton resonance peak at down field. In addition, in the polar effect of DMSO-d$_6$ makes 4-pyridone tautomer was preferred and caused to show coupling with nitrogen proton adjacent. On the other hand, when DMSO-d$_6$ with CDCl$_3$ was using, nitrogen proton disappeared at this position, caused no coupled of carbon proton adjacent. In this case, the nitrogen proton may be easily labile.

The ^{13}C-NMR spectrum of 2-arylpyrazolo [4,3-c] quinolin -3-one (7a) (Figure 19) were assigned for 16 carbons, by DEPT - 135 could be identified for C-H in this molecule as following, the peak at 118.75 ppm for two carbons at position 12 and 16, the peak at 128.73 ppm for two carbons at position 13 and 15. The chemical shifts at

119.60, 122.19, 130.24, 126.52, 124.05 and 139.41 ppm represented carbons at position 14, 6, 5, 7, 8 and 1 respectively. For remained carbon peak could be assigned as quaternary carbon in molecule as following, the peak at 142.07 ppm represented two carbons at position 3 and 11. The chemical shifts at 106.23, 135.31 and 140.15 ppm represented for carbons at position 2, 4 and 9 respectively. The carbonyl carbon for amide showed at 161.70 ppm. The data of ^{13}C-NMR and ^{1}H-NMR were summarized in Table V.
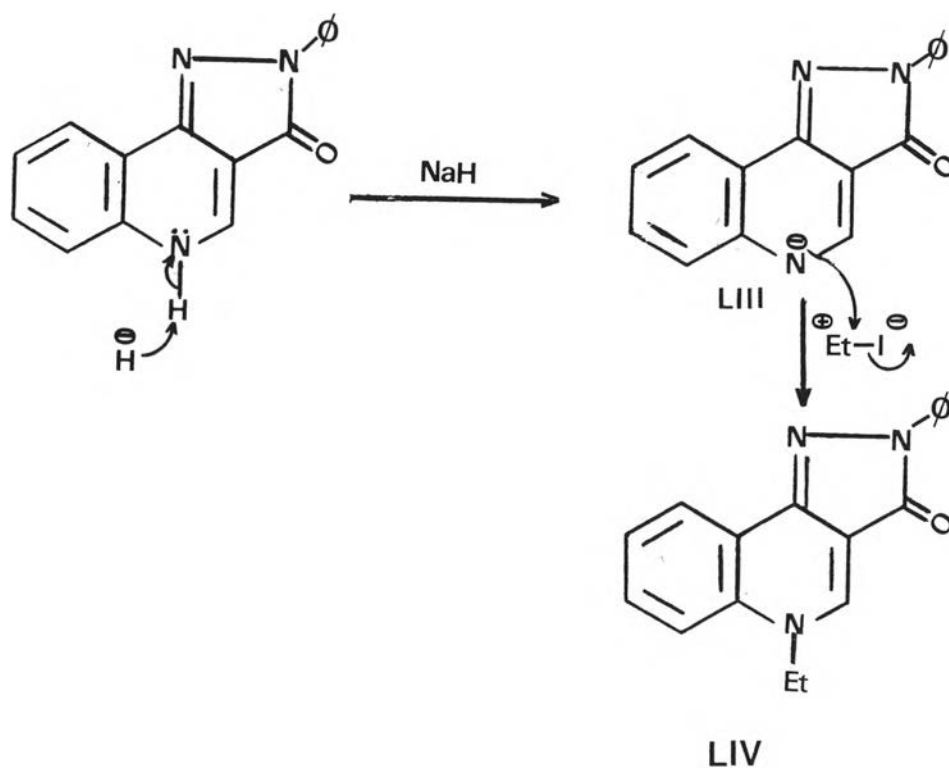
d) <u>5-Ethyl-2-arylpyrazolo [4, 3-c] quinolin-3-one</u> (8a)

The synthesis of 8a was accomplished by N-alkylation reaction of 2-arylpyrazolo [4, 3-c] quinolin - 3-one and ethyl iodide in tetrahydrofuran in the presence of sodium hydride. 2-Arylpyrazolo [4,3-c] quinolin -3-one nucleus exists in three possible tautomeric forms, as shown in scheme II ; therefore, all three forms could be carried out alkylation. Nevertheless, in this condition produced the preferable product, 5-ethyl-2-aryl-pyrazolo [4, 3-c] quinolin -3-one.
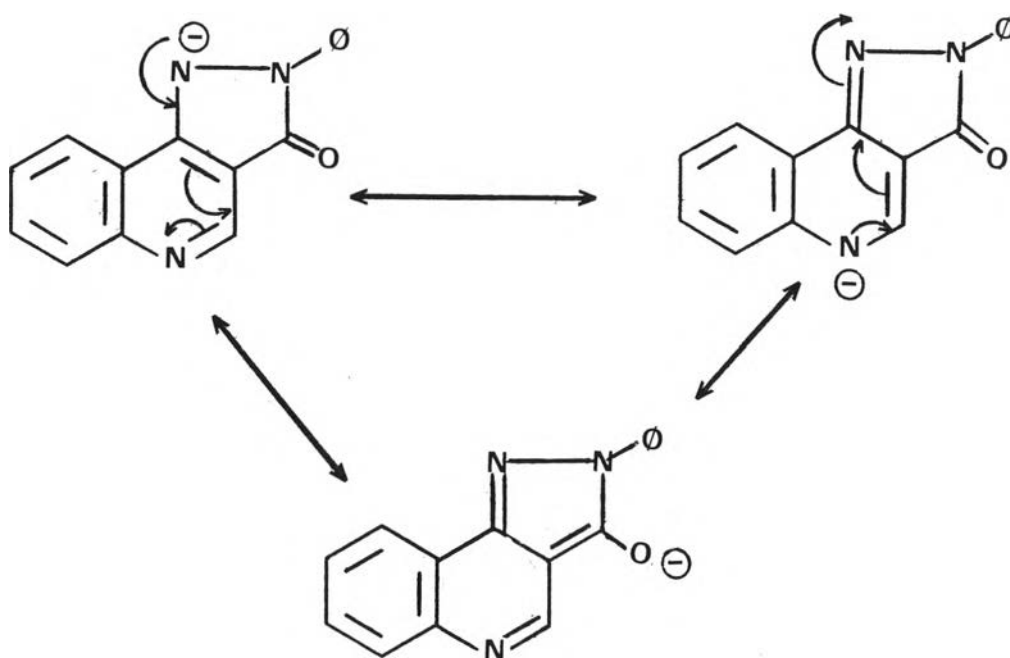
Scheme II : Isomerization of Ionized form of 2-arylpyrazolo [4,3-c] quinolin -3-one.

The reaction mechanism involved electrophilic attacks of ethyl group contained positive charge to electron on nitrogen of pyrazoloquinolone (LIII) from which made to attract nitrogen proton by sodium hydride, and the corresponding 5-ethyl-pyrazoloquinolone as following.

The IR spectrum of 5-ethyl-2-arylpyrazolo [4,
3-c] quinolin -3-one (8a) (Figure 27) showed the peaks of
C-H stretching vibration between 2974 - 3034 cm^{-1}, the
strong peak at 1640 cm^{-1} for C=O stretching vibration of
amide, peak at 1604 cm^{-1} for C=N stretching vibration, the
scissoring band of C-H at 1490 cm^{-1}. The ^{1}H-NMR spectrum
of 8a (Figure 28) showed at peak 1.43 ppm (triplet, 3H)
for methyl protons, at peak 4.51 ppm (quartet, 2H) for
methylene protons, at peak 7.71 ppm (triplet, 1H) for
phenyl proton para to nitrogen amide, the peak at 7.45 ppm
(triplet, 2H) for two phenyl protons meta to nitrogen

amide, the peak at 7.61 ppm (triplet, 1H) for aromatic proton (in quinoline ring) para to nitrogen atom, the peak at 7.76 ppm (triplet, 1H) for proton meta to pyridine fused, the peak at 7.94 ppm (doublet, 1H) for proton ortho to pyridine fused, the peak at 8.20 ppm (doublet of doublets, 2) for two phenyl protons ortho to nitrogen amide, the peak at 8.3 ppm (doublet, 1H) for proton ortho to pyridine fused and the peak at 8.9 ppm (singlet, 1H) which assigned as aromatic proton adjacent pyridine nitrogen.

The ^{13}C-NMR spectrum of 5-ethyl-2-aryl pyrazolo [4, 3-c] quinolin -3-one (8a) (Figure 21) represented for 18 carbons which were assigned as following, the peak at 119.94 ppm represented carbon at position 16 the peak at 128.76 ppm for two carbons at position 15 and 17, the peak at 143.45 ppm for two carbons at position 5 and 13. The chemical shifts at 14.61, 48.77, 106.35, 118.05, 118.71, 119.94, 130.59, 124.10, 126.61, 122.82, 135.33, 140.09 and 142.77 ppm represented carbons at position 1, 2, 4, 18, 14, 7, 8, 9, 10, 6, 3, 11 and 12 respectively. The carbonyl carbon for amide showed at 161.70 ppm. The data of ^{13}C-NMR and ^{1}H-NMR were summarized in Table VI.

The mass spectrum of 8a (Figure 30) showed peak at m/e 289 for molecular ion peak. The fragment ion peak at m/e 260 exhibited the loss of C_2H_5 group (mass = 29). The characteristic peak at m/e 102, 105, 145 and 156 indicated that ethylation reacted at position N-5 of pyrazoloquinolone ring which this fragmentation was proposed as following.
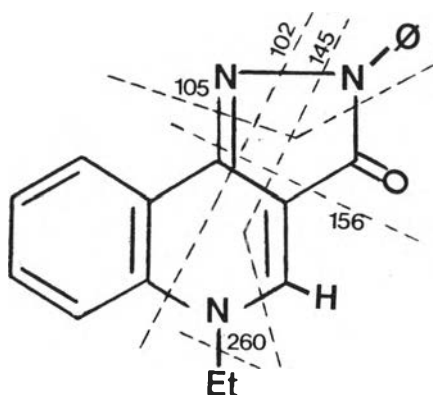
The desired pyrazoloquinolone derivatives were synthesized either directly according to or by slight modification of 5-ethyl -2-arylpyrazolo [4, 3-c] quinolin -3-one (8a). This synthesis contained :

1.   The synthesis of 3-carboethoxy -7 chloro-6-fluoro-4-hydroxyquinoline

2.   The synthesis of 3-carboethoxy -4,7-dichloro - 6-fluoro- quinoline

3.   The synthesis of Pyrazoloquinolone derivatives

4.   N-ethylation of Pyrazoloquinolones derivatives

5.   Synthesis of (7-piperazinyl) Pyrazoloquinolone derivatives

3- Carboethoxy -7-chloro -6-fluoro -4- hydroxyquinoline (5b)

The synthesis of 5b started by reaction of diethyl ethoxymethylenemalonate with 3-chloro -4-fluoroaniline the corresponding ethyl anilino (-3-chloro -4-fluoro) methylenemalonate (4b). Cyclization of 4b in diphenyl ether at 260 $^\circ$ gave 5b. The chemical structure of 4b and 5b determined by using IR and ^{1}H- NMR spectrometric technique.

The IR spectrum of Ethyl anilino (3-chloro-4-fluoro) methylenemalonate (4b) (figure 6) exhibited characteristic of ester group by showed carbonyl peak at 1720 cm^{-1} and strong peak at region 1150 - 1300 cm^{-1} for C-O stretching vibration. More, the peak at 1650 cm^{-1} was observed which could be interpreted as C=C stretching vibration, the N-H stretching was found at 3100-3450 cm^{-1} and N-H bending at 1618 cm^{-1}.

The ^{1}H-NMR spectrum of Ethyl anilino (3-chloro-4-fluoro) methylenemalonate (4b) (Figure 7) exhibited the characteristic proton of two ester groups at 1.21 ppm (multiplet, 6H) and 4.05 ppm (multiplet, 4H). The aromatic hydrogen atom adjacent to fluorine atom was found at 7.3 ppm (doublet of doublets, 2H, J_{value} = 7.7 Hz) which having lesser coupling constant than aromatic hydrogen atom adjacent to chlorine atom at 7.62 ppm (doublet, 1H, J_{value} = 6.9 Hz). The hydrogen attached to the olefin carbon was showed at 8.18 ppm (doublet, 1H, J_{value} = 13.8 Hz) and the proton chemical shift of N-H group presented at 10.51 ppm (broad, 1H, J_{value} = 13.5 Hz).

The condensation reaction stage of ethyl anilino (3-chloro-4-fluoro) methylenemalonate was possible two directions, as -para (LVIa) and -ortho (LVIb) to the chlorine atom. As ring closure of this compound occurred ortho to the chlorine atom, the 5-chloro-6-fluoroquinoline isomer would result (Fernandes, 1989). Compound 6b can be assigned from the ^{1}H-NMR spectra, but no 5-chloro-6-fluoroquinoline was obtained because of the ortho coupling was disappeared. This result was probably due to a steric hindance of chlorine atom.
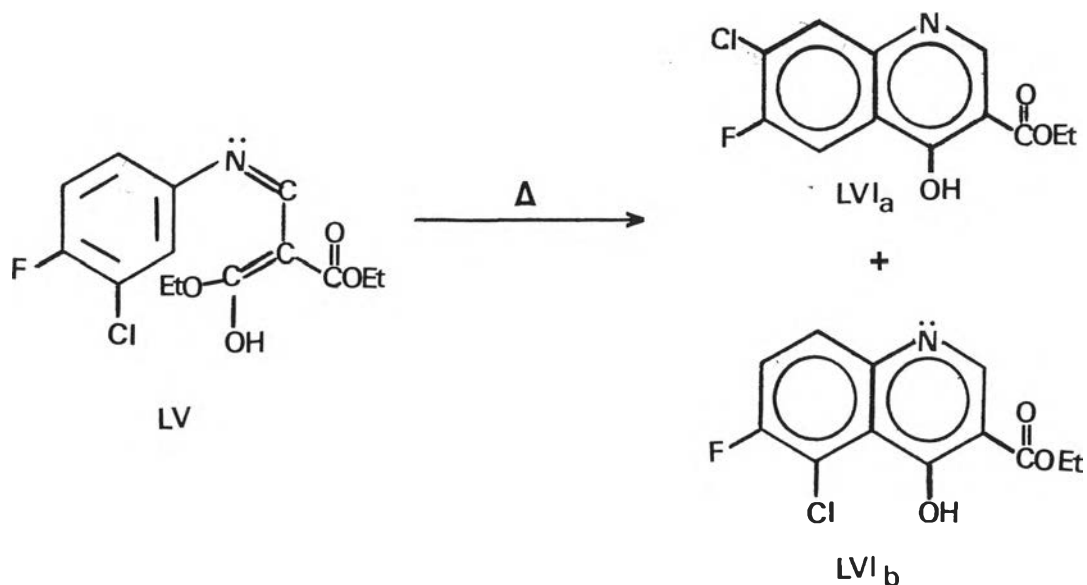
The IR spectrum of 3-carboethoxy-7-chloro -6-fluoro -4-hydroxyquinoline (5b) (Figure 10) showed carbonyl absorption peak at 1700 cm^{-1} for C=O stretching vibration and the peak at 1180, 1370 cm^{-1} for C-O stretching vibration. In addition, the peak at 1610 cm^{-1} for C=N stretching vibration, the peak at 1464 cm^{-1} for

C-H bending vibration, the peak at 1382 cm^{-1} for O-H bending

vibration and peak of C-H stretching vibration at region

2890 - 3150 cm^{-1} The ^{1}H-NMR spectrum of 5b (Figure 11)

showed the peak at 1.38 ppm for methyl protons (triplet,

3H) the peak at 4.44 ppm for methylene protons (quartet,

2H). The chemical shift at 8.31 ppm and 8.49 ppm were

assigned as aromatic protons adjacent to fluorine atom

(doublet, 1H, J_{value} = 9.6 Hz) and chlorine atom (doublet,

1H, J_{value} = 6.4 Hz) respectively. The peak at 9.17 ppm

was represented for proton adjacent nitrogen atom in

pyridine system. In the ^{1}H-NMR spectrum, a signal for a

O-H proton disappeared which was explained by

tautomerization of this molecule.

3-Carboethoxy -4,7-dichloro-6-fluoro-quinoline (6b)

The intermediates 6b was prepared by chlorination

of 3-carboethoxy -7-chloro-6-fluoro -4-hydroxy quinoline.

The IR spectrum of 3-carboethoxy -4, 7-dichloro-6-

fluoro-quinoline (6b) (Figure 14) showed the peak at 1729

cm^{-1} for C=O stretching vibration of carbonyl ester and

peak at 1194 cm^{-1} for C-O stretching vibration. In

addition, the peak at 1581 cm^{-1} was identified for C=C

stretching vibration and peak at 1471 cm^{-1} for C-H bending (CH$_2$CH$_3$). The ^{1}H-NMR spectrum of 6b (Figure 15) showed characteristic peak of ester group at chemical shifts 1.44 ppm for methyl protons (triplet, 3H) and 4.47 ppm for methylene protons (quartet, 2H), the peak at 8.14 ppm and 8.22 ppm which are represented for aromatic protons adjacent to fluorine atom (doublet, 1H, J_{value} = 9.6 Hz) and chlorine atom (doublet, 1H, J_{value} = 6.4 Hz) respectively. The proton adjacent to nitrogen atom in pyridine system was assigned at chemical shift 9.15 ppm (singlet, 1H).

The synthesis of Pyrazoloquinolone derivatives

The next reaction of 3-carboethoxy -4, 7-dichloro -6-fluoro-quinoline intermediate was carried out with amine nucleophile, as phenylhydrazine or hydrazine. When, this molecule is considered, the fact that both of the chlorine bearing carbon atoms are potentially susceptible to nucleophilic attack but only substitution at the 4-position results in the desired product. The high selectivity that is actually observed for reaction at the 4-position. A basis for the necessary difference can be seen by consideration of the relative stabilities of

the charged intermediates from attack of an amine at C-4 and C-7. The nitrogen atom is able to stabilize the negative charge in intermediate (LVII) without complete disruption of aromaticity, whereas the corresponding stabilization in (LIXa) does not allow for retention of aromaticity, illustrated as following. Consequently (LVII) and the transition state leading to it are lower in energy than LIX and its corresponding transition state. The result, then, is that 7-position has low reactivity toward nucleophilic aromatic substitution whereas the 4-position is quite reactive toward such a reaction.
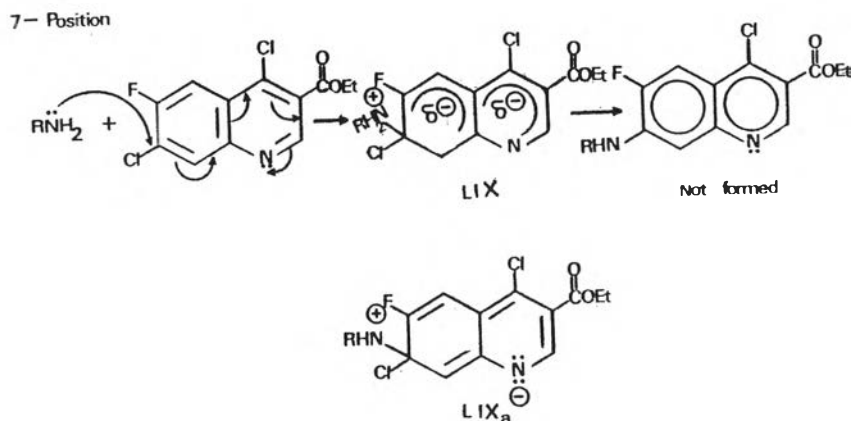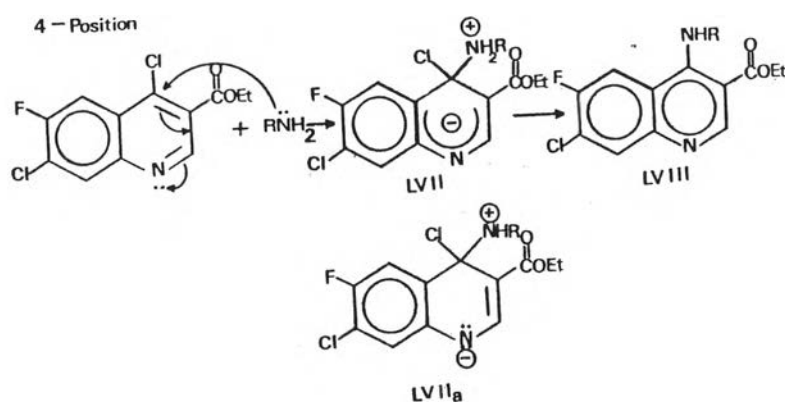
1.   7-Chloro-8-fluoro-2-arylpyrazolo [4,   3-c]
quinolin -3-one. (7b)

Compound 7b represents model in pyrazoloquinolone
series with phenyl group substituted N-2.   7b   was
synthesized   in   similar   fashion   to   the   2-
arylpyrazoloquinolone (7a).   However, the desired 7-
chloro-8-fluoro-2-arylpyrazoloquinolones is precipitated
in xylene which is easily for the separation by
filtration.

The   IR   spectrum   of   7-chloro-8-fluoro-2-
arylpyrazolo [4,   3-c] quinolin -3-one (7b) (Figure   21)
showed the peak at 1627 cm^{-1} for C=O stretching vibration,
the peak at 1610 cm^{-1} for C=N stretching vibration, the
peak at 1588 cm^{-1} for C=C stretching vibration, the peak
at 1362 cm^{-1} for C-N stretching vibration which the
absorption appeared at higher frequency because the force
constant of the C-N band is increased by resonance with
the ring.   The ^{1}H-NMR spectrum of 7-chloro-8-fluoro-2-
arylpyrazolo [4,   3-c] quinolin -3-one (7b) (Figure   12)
showed chemical shift at 7.19, 7.45 and 8.21   ppm   which
were represented for para proton (triplet, 1H), two meta
protons (triplet, 2H) and two ortho protons (doublet, 2H)

respective of phenyl group. The chemical shift at 7.89 and 8.15 ppm was assigned as two aromatic proton adjacent to chlorine (doublet, 1H, J_{value} = 6.5 Hz) and fluorine (doublet, 1H, J_{value} = 9.3 Hz), respectively. The peak at 8.81 ppm (singlet, 1H) represented proton adjacent nitrogen atom in pyridine system.

2. 7-Chloro-8-fluoro-2H-pyrazolo [4,3-c] quinolin -3-one (7c)

Compound 7c represents pyrazoloquinolone without substituent at position 2 (R=H). The 3-carboethoxy-4, 7-dichloro-6-fluoro-quinoline was allowed to react with alcoholic hydrazine solution (freshly generated from hydrazine sulfate in sodium ethoxide) in the presence of sodium ethoxide at room temperature to afford the desired 7-chloro-8-fluoro-2H-pyrazolo [4, 3-c] quinolin -3-one.

The IR spectrum of 7-chloro-8-fluoro-2H-pyrazolo [4, 3-c] quinolin -3-one (7c) (Figure 25) showed the peak region 2950 - 3030 cm^{-1} for C-H stretching vibration strong absorption peak of amide carbonyl at 1327 cm^{-1}, the peak of C=C stretching vibration at 1585 and at 1312 cm^{-1} for C-N stretching vibration which indicated characteristic of secondary amide. The ^{1}H-NMR of 7-chloro-8-fluoro-2H –

pyrazolo [4, 3-c] quinolin -3-one (7c) (Figure 26) showed two signals at chemical shift 7.87 and 7.95 ppm for aromatic proton adjacent to chlorine atom (doublet, 1H, J_{value} = 6.9 Hz) and to fluorine atom (doublet, 1H, J_{value} = 9.6 Hz). The shielding chemical shift at 8.61 ppm was explained usual origin for proton adjacent nitrogen atom on pyridine system. In obvious proton spectra no having two nitrogen protons signal by means of active protons which easily labiled.

## N-ethylation of Pyrazoloquinolone derivatives

Treatment of 7-chloro -8-fluoro -2-arylpyrazolo [4,3-c] quinolin -3-one (7b) with ethyl iodide in the presence of sodium hydride in dry tetrahydrofuran readily gave 7-chloro-5-ethyl -8-fluoro -2-arylpyrazolo [4,3-c] quinolin -3-one (8b). This addition reaction is also applicable to 7-chloro-8-fluoro -2H-pyrazolo [4,3-c] quinolin -3-one (7c) which give 8c.

7-Chloro-5-ethyl -8-fluoro-2-arylpyrazolo [4,3-c] quinolin -3-one (8b)

The IR spectrum of 7-chloro-5-ethyl -8-fluoro -2-arylpyrazolo [4, 3-c] quinolin -3-one (Figure 31) showed

amide carbonyl at 1650 cm^{-1}, peak at 1641 cm^{-1} for C=N stretching vibration, peak at 1591 cm^{-1} for C=C stretching vibration, peak at 1466 cm^{-1} for C-H bending of CH_2CH_3 group and peak at 1309 cm^{-1} for C-N stretching vibration. The ^{1}H-NMR spectrum of 7-chloro-5-ethyl -8-fluoro-2-arylpyrazolo [4, 3-c] quinolin -3-one (Figure 32) showed ester group identified at chemical shifts 1.40 ppm (triplet, 3H) for methyl proton and 4.51 ppm (quartet, 2H). In similar with proton spectra of 7-chloro-8-fluoro-2-arylpyrazolo [4, 3-c] quinolin-3-one, the signals at 7.20, 7.46, 8.18 ppm was assigned to phenyl ring. The chemical shift at 8.23 and 8.27 ppm was identified for aromatic proton adjacent to fluorine atom (doublet, 1H, J_{value} = 9.6 Hz) and chlorine atom (doublet, 1H, J_{value} = 6.4 Hz), respectively and peak at 8.91 ppm for aromatic proton adjacent to nitrogen atom in pyridine system.

The site of N-5 ethylation but not N-1 ethylation can be detected by the MS. Mass spectra of 8b (Figure 33) characterized by molecular ion at m/e 341 and showed fragment ion peak at m/e 105, 208, 221 and 222 which was purposed as following. More, the characteristic peaks at m/e 306 and 312 represented the loss of chlorine atom (mass = 35) and ethyl group (mass = 29) respectively.
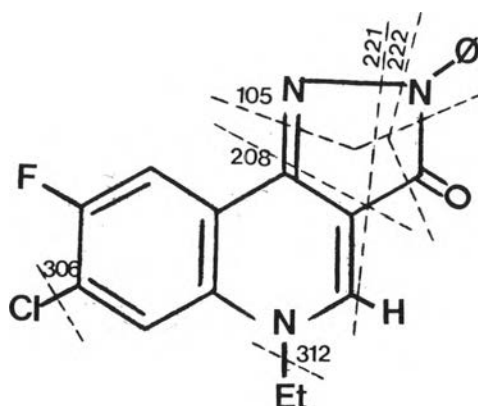
7-Chloro-5-ethyl -8-fluoro-2H-pyrazolo [4,3-c]
quinolin -3-one (8c)

The 7-chloro-8-fluoro -2H-pyrazolo [4, 3-c]
quinolin-3-one can be exist in six possible tautomeric
forms as shown in scheme III.
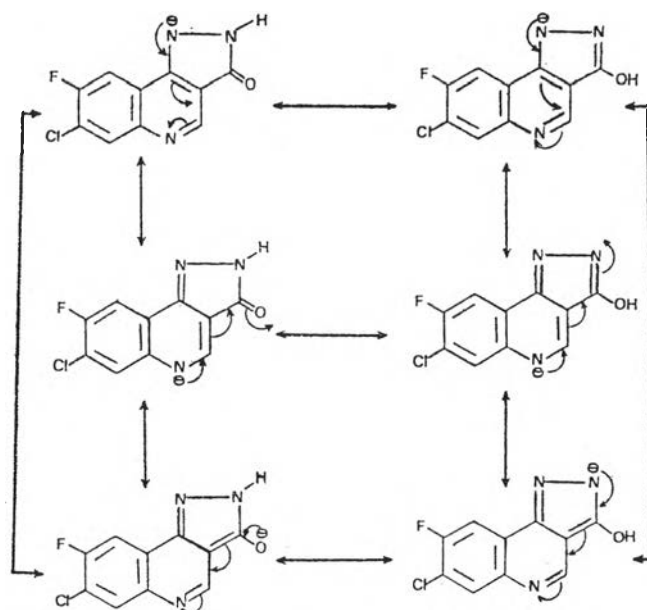
Scheme III : Isomerization of Ionized form of 7-
chloro-8-fluoro -2H-pyrazoloquinolin -3-one.

Thus, the attempt instead of ethylation taking on nitrogen produced a complicated mixture of products. Here, the ease of ethylation products depending upon the reaction conditions. As the desired 5-ethyl-substituted predominated under this reaction condition.

The IR spectrum of 7-chloro-5-ethyl-8-fluoro-2H-pyrazolo [4, 3-c] quinolin -3-one (8c) (Figure 34) characterized of C-H aromatic at 3608 - 3138 cm^{-1} and 2955 - 2860 cm^{-1} for C-H of CH_2CH_3 group, the strong peak at 1628 cm^{-1} for amide carbonyl, the peak at 1523 cm^{-1} for C=C stretching vibration, the peak at 1465 cm^{-1} for C-H bending vibration (CH_2CH_3) and the peak at- 1379 cm^{-1} for C-N streching vibration. The ^{1}H-NMR of 7-chloro-5-ethyl-8-fluoro-2H-pyrazolo [4, 3-c] quinolin-3-one (8c) (Figure 35) showed peak at 1.43 ppm (triplet, 3H) for methyl protons, the peak at 4.50 ppm for methylene protons, the peak at 8.06 and 8.17 ppm for proton adjacent to fluorine atom (doublet, 1H, J_{value} = 11.2) and to chlorine atom (doublet, 1H, J_{value} = 6.4), respectively. The chemical shifts at 8.70 ppm (singlet, 1H) for proton adjacent to nitrogen on pyridine system and the broad peak at 11.54 ppm (broad, 1H) for N-H proton. The mass spectra (Figure 36) was made also to confirm this structure according

to molecular ion peak at m/e 265. The fragment ion peak showed at m/e 154, 180, 209 and 230 which shown as below.
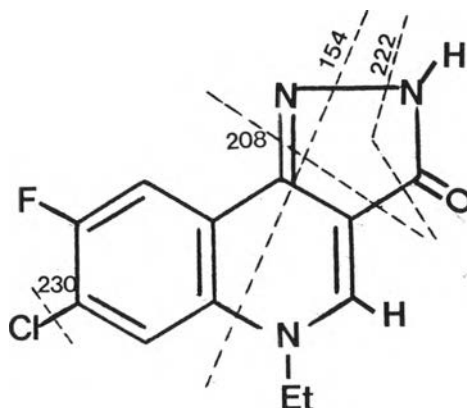
The location of the N-ethyl, 1-ethyl and 5-ethyl isomers are confirmed on the basis of NMR data. A shielding effect was evident for aromatic proton adjacent to nitrogen of 8.70 and 9.04 ppm. The resonance was shifted downfield compared to the corresponding signals in 1-ethyl isomer. Moreover, in two compounds the proton of the two ethylic groups present a little difference chemical shift of 4.50 and 4.6 ppm, this suggests that the quinoline nitrogen (N-1) exert deshielding effect on it.

Interestingly, N-ethylated of 7c produced much more the other compounds, depending upon the conditions of the reaction. Using sodium hydride and ethyl iodide gave

the N-5 ethylated (8c) and N-1 ethylated derivatives as major and minor product, respectively. When 7c was allowed with ethyl iodide in an ethanolic solution in the presence of potassium carbonate under reflux the corresponding 1, 3 and 2, 5 diethyl derivatives were isolated. But the N-1 or 5 ethylated derivatives were only formed in negligible yield.

The IR, ^{1}H-NMR and mass spectra of compound N-1 ethylated, 1, 3 and 2, 5 diethyl isomer confirmed the structures assigned (Table 2). The proton spectra these compounds showed for the N-substituents and in the aromatic region (H-4, H-6 and H-9).

7-Chloro-1-ethyl -8-fluoro -2H-pyrazolo [4, 3-c] quinolin -3-one

The IR spectrum of 7-chloro-1-ethyl-8- fluoro -2H-pyrazolo [4,3-c] quinolin -3-one (Figure 43) showed peak at region 2893-2907 cm^{-1} for C-H stretching vibration, the strong peak at 1636 cm^{-1} for amide carbonyl, C=C stretching vibration at 1591 cm^{-1}, C-H bending vibration (CH_2CH_3) at 1437 ppm, C-N stretching vibration at 1345 cm^{-1}. The ^{1}H-NMR (Figure 44) showed peak at chemical

shift 1.42 ppm (triplet, 3H) for methyl protons, the peak at 4.61 ppm for methylene protons, the peak at 8.36 ppm (doublet, 1H, J_{value} = 9.1) and 8.31 ppm (doublet, 1H, J_{value} = 6.6) for proton adjacent to fluorine atom and chlorine atom, respectively. The chemical shifts at 9.04 ppm (singlet, 1H) for proton adjacent to nitrogen on pyridine. This, support for quinoline structure of N-1 ethylated with downfield shift of 4-H was assigned when compared with 4-H signal of 8c (5-ethyl) which appears at 8.70 ppm. The mass spectra (Figure 45) was confirmed with molecular ion peak at m/e to 265 which was similar to N-5 ethylated isomer.

7-Chloro-3-ethoxy -1-ethyl-8-fluoro- 2H-pyrazolo [4,3-c] quinoline

The IR spectrum of 7-chloro-3- ethoxy-1-ethyl -8-fluoro -2H-pyrazolo [4,3-c] quinoline (Figure 47) showed peak at 2890 - 3113 cm^{-1} for C-H stretching vibrations, the peak at 1616 cm^{-1} for C=N stretching vibration, C=C stretching vibration at 1576 cm^{-1}, C-H bending vibration (CH_2CH_3) at 1467 cm^{-1}, and C-N stretching vibration at 1348 cm^{-1}. The ^{1}H-NMR (figure 48) showed peak at 1.40 ppm (multiplet, 6H) for two methyl protons. The peak at 4.42

ppm (quartet, 2H) represented ethoxy protons and also confirmation disappeared of amide carbonyl absorption in the IR spectra. The peak at 4.65 ppm (quartet, 2H) should be methylene protons adjacent nitrogen at position 1. The peak at chemical shift 8.30 ppm (doublet, 1H J_{value} = 9.3 Hz) proton adjacent to fluorine atom and chlorine atom, respectively. The peak at 8.94 ppm represented proton adjacent to nitrogen on pyridine. The mass spectra (Figure 49) was showed peak at m/e 293 for molecular ion peak.

7-Chloro-2, 5-diethyl -8-fluoro-pyrazolo [4,3-c] quinolin -3-one

The IR spectrum of 7-chloro-2, 5-diethyl -8-fluoro-pyrazolo [4,3-c] quinolin -3-one (Figure 50) showed peak at 2806-3105 cm^{-1} for C-H stretching vibration, the peak at 1644 cm^{-1} for amide carbonyl, C-H bending vibration at 1463 and C-N stretching vibration at 1369 cm^{-1}. The ^{1}H-NMR (Figure 51) showed peak at 1.24 ppm (triplet, 3H) for methyl proton in ethyl amide and the peak at 1.35 ppm (triplet, 3H) for methyl protons in ethylenic group at position N-1. The peak of proton at 3.90 ppm (quartet, 2H) should be methylene protons of ethyl amide by observed

for a greater high field shift. The peak at chemical shift 4.47 ppm (quartet, 2H) represented methylene proton of ethyl group at N-1, The peak of· proton adjacent to fluorine atom at 8.03 ppm (doublet, 1H,· J_{value} = 9.3 Hz), doublet of proton adjacent to chlorine atom at 8.18 ppm (doublet, 1H, J_{value} = 6.4 Hz) and singlet of proton adjacent nitrogen atom at 8.76 ppm (singlet, 1H). The mass spectrum (Figure 52) showed peak with the same 1, 3-diethyl isomer at m/e 293 for molecular ion peak.

Attempt to synthesis of 7-(1-piperazinyl) pyrazolo-quinolone (10a-b)

In the attempt to introduce the piperazinyl substituent into the desired position C-7, several conditions were employed.

Firstly, upon heating start 7b-c and piperazine in pyridine by upto 72 hours, the product was formed to the 8-piperazinyl (8b-c).

7-Chloro-5-ethyl-8-(1-piperazinyl)-2-arylpyrazolo [4,3-c] quinolin -3-one (8b)

The structure of 7-chloro-5-ethyl-8-(1-piper azinyl) -2-arylpyrazolo [4, 3-c] quinolin-3-one was confirmed on the basis of IR, ^{1}H-NMR and mass spectra.

The IR spectrum of 8b (Figure 37) showed peak at region 3300 cm^{-1} which was identified for N-H stretching vibration. The peak at 2820 - 3010 cm^{-1} for C-H showed stretching vibration, carbonyl absorption for the amide group at 1630 cm^{-1}, peak at 1590, 1469 and 1312 cm^{-1} for C=C stretching vibration, C-H bending vibration (CH$_2$CH$_3$) and C-N stretching vibration respectively. The ^{1}H-NMR spectrum of 8b (Figure 38) characterized lacking of the coupled adjacent protons signal (the presence of fluorine atom), and peak of piperazine protons (CH$_2$) at chemical shifts 3.10 ppm. This suggested that the piperazinyl group attacked at C-8 displacing fluorine atom. The retaining signals were consistent with 7-chloro-5-ethyl-2-arylpyrazolo [4, 3-c] quinolin -3-one structure, as showed chemical shifts at 1.47, 4.50, 7.42, 7.59, 7.90, 8.08, 8.23, 8.31 and 8.85 ppm for ethyl group, phenyl group and pyrazoloquinolone system. Additional confirmation of this

structural assignment was obtained by the identification of a mass spectral peak (Figure 39) corresponding to molecular ion peak at m/e 407, and fragment ion peaks at m/e 371 and 322 which were in agreement with loss of chlorine (mass = 35) and piperazinyl group (mass = 85), respectively.

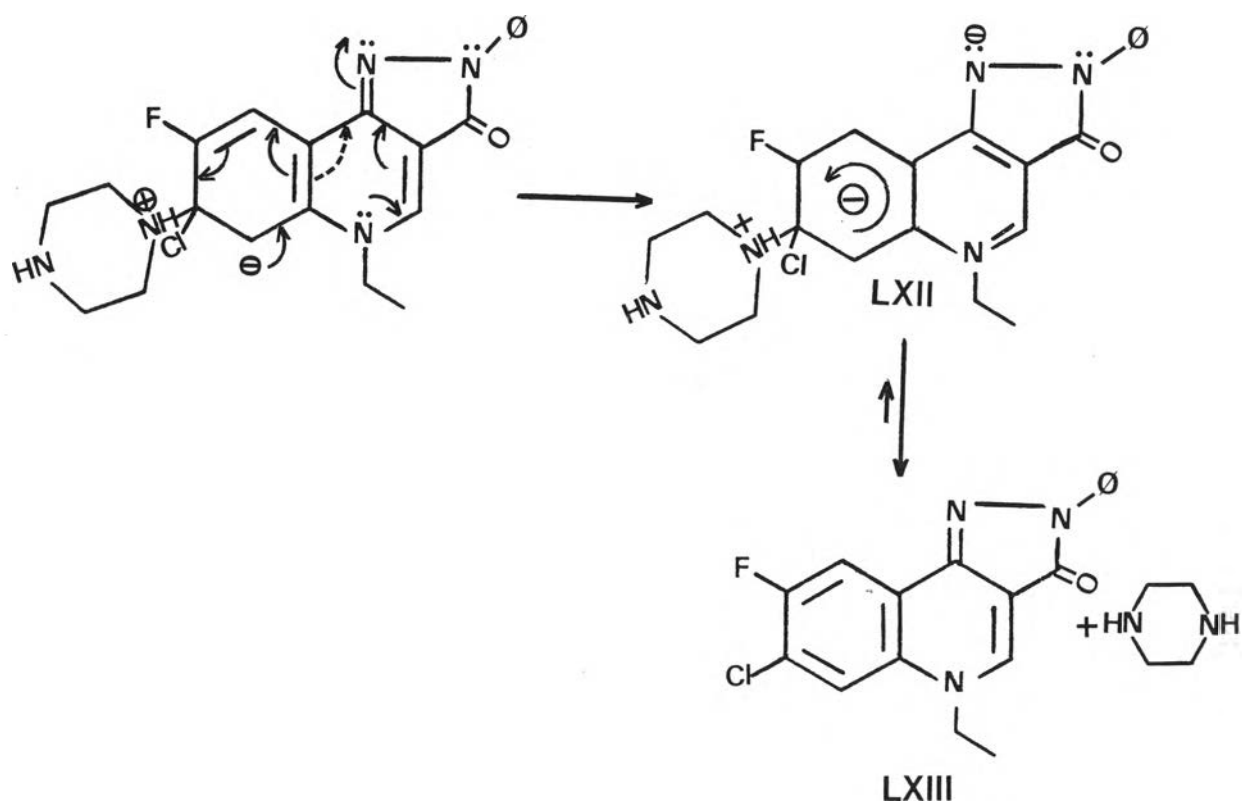7-Chloro-5-ethyl -8-(1-piperazinyl) -2H-pyrazolo [4,3-c] quinolin -3-one (8c)

The IR spectrum of 7-chloro-5-ethyl-8- (1-piperazinyl) -2H-pyrazolo [4, 3-c] quinolin -3-one (8c) (Figure 40) showed characteristic of N-H stretching vibration at 3406 cm^{-1}, the peak at 2930 - 3010 cm^{-1} for C-H stretching vibration, strong peak of carbonyl amide at 1620 cm^{-1}, the peak at 1519 cm^{-1} for C=C stretching vibration and the peak at 1469 cm^{-1} for C-H bending (CH_2CH_3). The ^{1}H-NMR spectrum of 8c (Figure 41) showed peak at chemical shift 1.30 ppm for methyl protons (triplet, 3H) the peak at 3.07 ppm for piperazine protons (CH_2) (multiplet, 8H), the peak at 4.42 ppm for methylene protons (quartet, 2H). The singlet peak at 7.68 and 7.95 ppm for aromatic proton adjacent to fluorine atom (singlet, 1H) and to chlorine atom (singlet, 1H)

respectively. In addition, the chemical shift at 8.62 ppm for aromatic proton adjacent nitrogen proton in pyridine system and at 11.49 ppm for N-H proton (broad, 1H). The mass spectrum of this compound (Figure 42) has molecular ion peak according to m/e at 331 and molecular ion peak at 295, 275, 56 abundance decreased respectively. The peak at m/e 36 and 85 represent lossing of chlorine atom and piperazinyl group respectively.

Altogether triethyl amine was added as base catalyst. The reaction was refluxed for several days, however 8-piperazinyl derivatives were formed. It might be the low nucleophilicity of piperazine rendered the nucleophilic reaction difficult. Therefore, zinc chloride was used activation pyrazoloquinolone. Also, no target product was detected.

The results showed that fluorine was preferable for the 8-substituent, the high selectivity must depend on a wide difference in the susceptibility toward nucleophilic substitution of the carbon atoms at position 7 and 8 in the molecule. As explanation for stabilities of the charged intermediate can be assumed. When, the amine attacks at C-7, the intermediate form (LXII) is

unable to stabilize and the nitrogen lone pair electrons of the ring makes the system less electrophilic render the reaction was difficult as shown in scheme IV. The result, the reaction at the C-7 position was not observed.

Scheme IV : Proposed Nucleophilic Substitution at C-7 position on 7-Chloro-5-ethyl -8-(1-piperazinyl) -2-arylpyrazolo [4,3-c] quinolin-3-one

On the other hand, when nucleophilic amine attacks to carbon position 8, the intermediate retarded reaction as well as at position 7 (negative charge located on

nitrogen atom) (LXIV). However, no the presence other
electron donating nitrogens were transfer at nitrogen
pyridine (Scheme V) hence the reaction occurred in this
way.
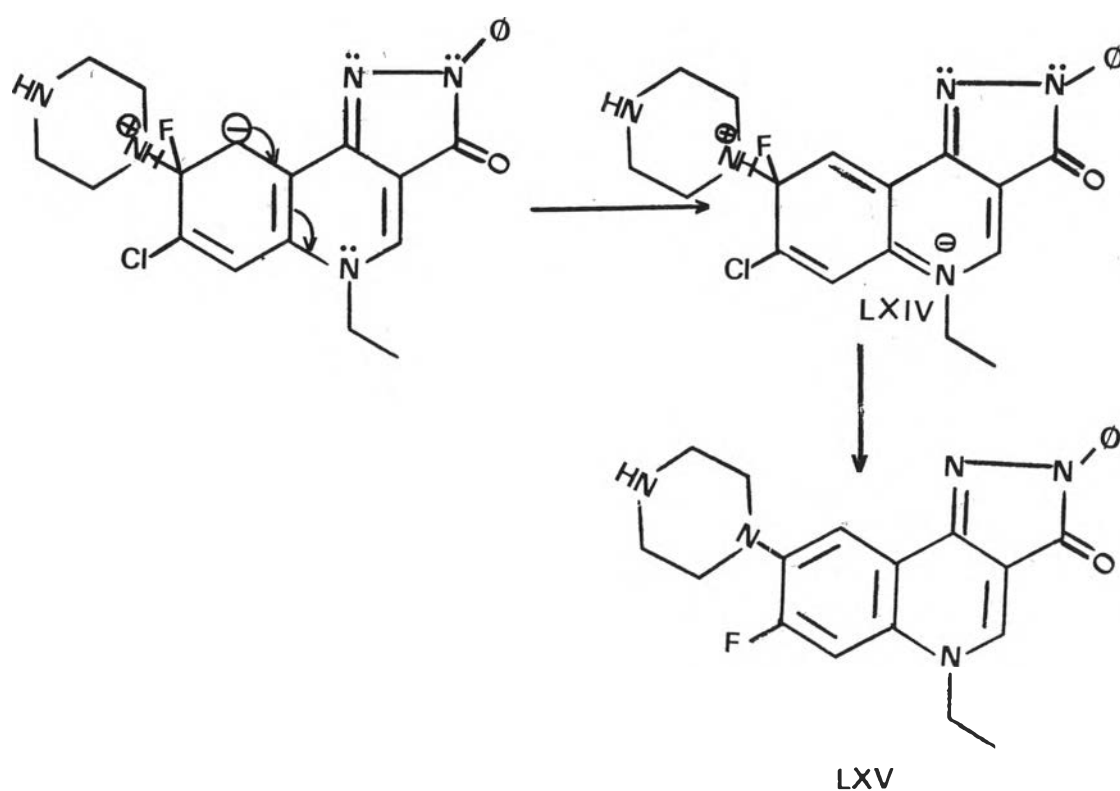
Scheme V : Proposed Nucleophilic Substitution at
C-8 position on 7-Chloro-5-ethyl -8-(1-piperazinyl) -2-
arylpyrazolo [4,3-c] quinolin-3-one

Thus, in order to decrease the presence of lone
pair nitrogen atom, the hydrochloric acid was hopeful
protonized a nitrogen atom. Although a longer reaction

period and a higher reaction temperature was used, no target product could be traced.

The another opinion according to the result was that the electronic effects of substituents at para position with chlorine atom, electron donating substituents prevent or retard, whereas electron withdrawing substituents facilitate the substitution. Based on these explanation the chloro atom of pyrazoloquinolones should be exchanged easily against nucleophiles by the influence of electron withdrawing, such nitro group (NO_2). Nevertheless, making has a limitation because the piperazine must be introduced at an early stage of the synthesis. By reduction and diazotization, nitro group was converted to the diazonium salt. The diazonium salt can be replaced by hydrogen and then, the reaction were carried out according to the preparation of pyrazoloquinolone.

In view of decreasing the presence of lone pair nitrogen atom ; such as at position N-5 has been likely to investigated. However, these must be further experimented.