PYRROLOQUINOLINES V[1]. 1H-PYRROLO[3,2-c]QUINOLINES

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This review deals with the known chemistry of pyrrolo[3,2-c]quinolines including their syntheses and spectra.

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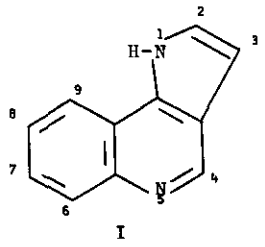
A. INTRODUCTION

The alkali-fusion of an indigo dye "Ciba yellow" gave a by product, characterized as indolo[3,2-c]quinoline, which on oxidation with chromic acid produced 1H-pyrrolo[3,2-c]quinoline-2,3-dicarboxylic acid. When heated above its melting point, the dicarboxylic acid underwent decarboxylation to give the parent ring system- 1H-pyrrolo[3,2-c]quinoline (I)[2]. Later on various other derivatives of



I

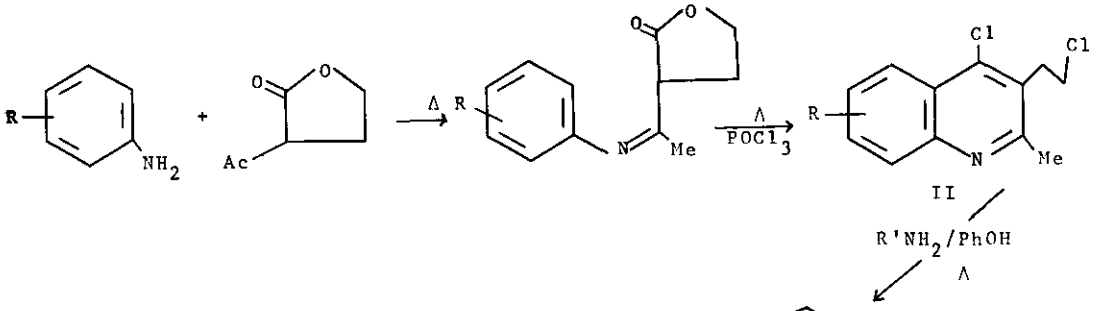
this newly discovered ring system were obtained from diverse reactions (see below).

B. SYNTHESES

B.1 Reduced 1H-pyrrolo[3,2-c]quinolines

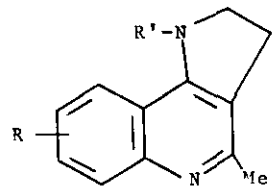
The Schiff bases derived from anilines and 2-acetylbutyrolactone when treated with phosphoryl chloride give 4-chloro-3-(2-chloroethyl)quinaldines (II) which when heated in phenol at temperatures ranging between 155 and 180° in the presence of different amines give rise to various 2,3-dihydro-1H-pyrrolo[3,2-c]-quinolines (III) (chart 1)[3-7]. The yields in these syntheses were variable (53 to 81%).

chart 1



R = H, 6-OMe, 7-OMe, 8-OMe, 6-OH, 7-OH, 8-OH, 6-OEt, 8-OEt, 8-MeNHCO, 6-Cl, 8-Cl, 9-OMe, 7,8(OEt)$_2$.

R' = H, Me, PhCH$_2$, Et$_2$NCH$_2$CH$_2$, CH$_2$CH$_2$OH, Ph, p-MeC$_6$H$_4$, o-MeOC$_6$H$_4$, m-MeOC$_6$H$_4$, p-MeOC$_6$H$_4$, o-ClC$_6$H$_4$, o-HOC$_6$H$_4$, m-HOC$_6$H$_4$, p-HOC$_6$H$_4$.

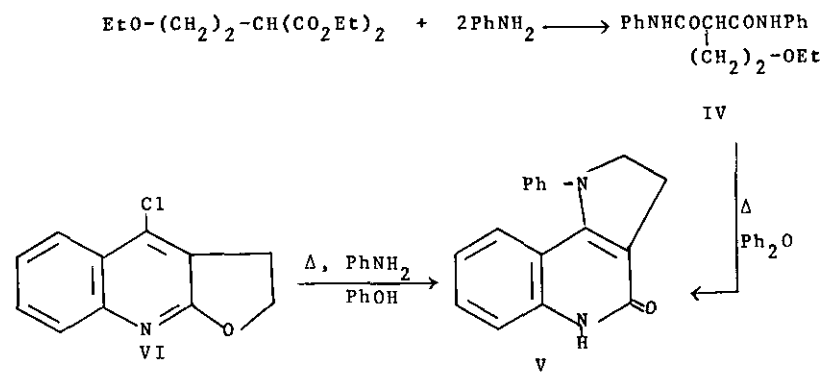


III

During the investigations of the reactions of substituted malonic esters,

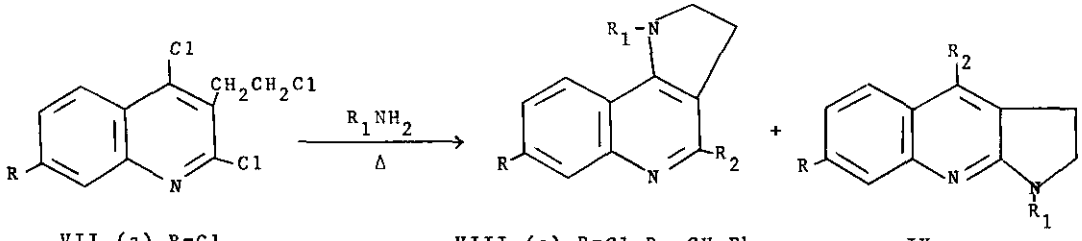
the dianilide (IV) obtained from aniline and ethyl (2-ethoxyethyl)malonate on heating in diphenyl ether cyclized to give 2,3-dihydro-1-phenyl-1H-pyrrolo[3,2-c]-quinolin-4-one (V) in 59% yield (chart 2). The structure of V was established by its transformation into other derivatives (see section B.2) as well as its synthesis from 2,3-dihydrofuro[2,3-b]quinoline (VI)[8].

chart 2



In another reaction 2,4,7-trichloro derivative of 3-(2-chloroethyl)-quinoline (VIIa) when made to react with benzylamine gave 1-benzyl-4-benzylamino-7-chloro-2,3-dihydro-1H-pyrrolo[3,2-c]quinoline (VIIIa) in 13% yield together with 28.6% of the isomeric 2,3-dihydro-1H-pyrrolo[2,3-b]quinoline (IX). A similar reaction of VIIb with ammonia gave a very low yield (3.5%) of VIIIb (chart 3)[9].

chart 3



VII (a) R=Cl
(b) R=OMe

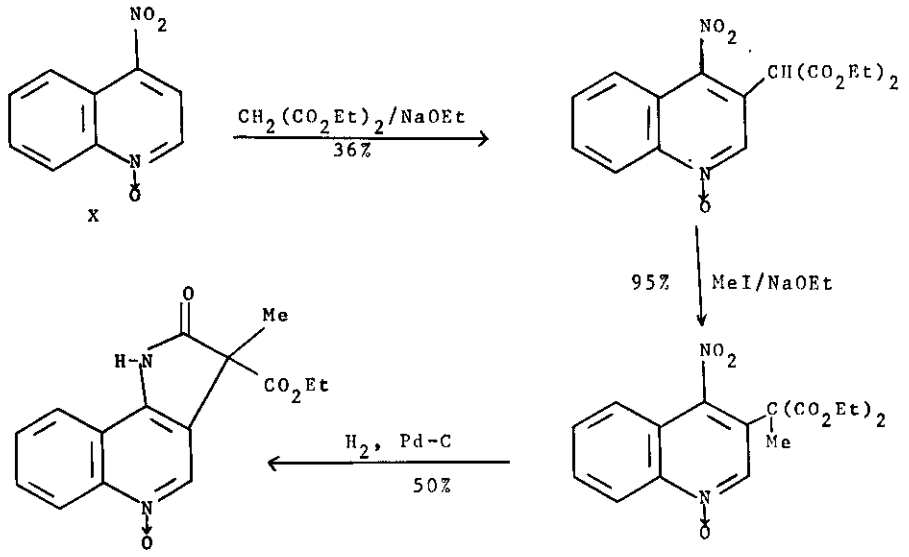
VIII (a) R=Cl, R_1=CH_2Ph, R_2=$HNCH_2Ph$
(b) R=OMe, R_1=H, R_2=Cl

IX R=Cl, R_1=CH_2Ph, R_2=$HNCH_2Ph$

4-Nitroquinoline 1-oxide undergoes interesting reactions with the carbanion derived from malonic ester and with isobutyraldehyde enamines. The substitution takes place at the 3 position of the quinoline with ring closure involving the nitro group thus leading to the formation of 2,3-dihydro-1H-pyrrolo-

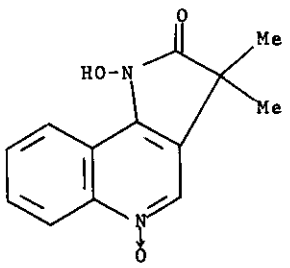
[3,2-c]quinolines. Thus when 4-nitroquinoline 1-oxide (X) was treated with diethyl sodiomalonate, the reaction occurred at the 3 position of quinoline instead of the expected nucleophilic substituition of the 4-nitro group. Successive alkylation and reduction furnished ethyl 2,3-dihydro-3-methyl-2-oxo-1H-pyrrolo[3,2-c]quinoline-3-carboxylate 5-oxide (XI) (chart 4)[10]. In another reaction X, under mild

chart 4

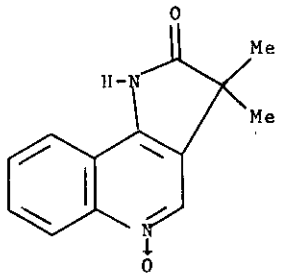


X XI

conditions, on treatment with a chloroform solution of isobutyraldehyde enamines gave 49% yield of 2,3-dihydro-3,3-dimethyl-1-hydroxy-1H-pyrrolo[3,2-c]quinolin-2-one 5-oxide (XII). In some reactions XIII was also isolated in yields ranging between 9 and 22%. The mechanism postulated for this reaction is given in chart 5.

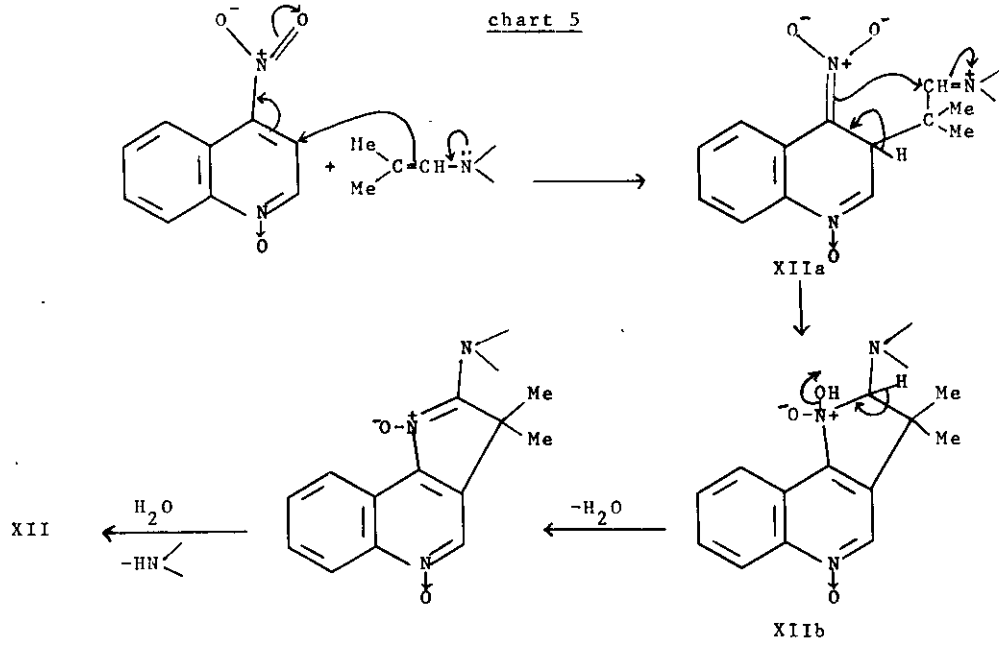


XII



XIII

chart 5



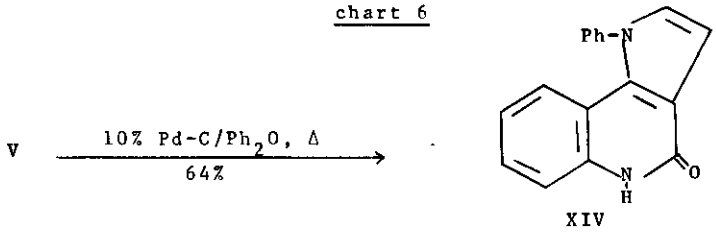
According to this mechanism proton elimination and N-C bond formation between the nitrogen atom of the nitro group and the immonium carbon proceed in a concerted manner from the intermediate XIIa and thus leading to XIIb which in successive steps gives XII (cf benzimidazole N-oxide formation from N,N-disubstituted o-nitroanilines via an aci-nitro intermediate[13]). Conducting this reaction at higher temperatures (refluxing in dichloromethane) or at room temperature in N,N-dimethylformamide or in tetrahydrofuran gave XIII in good yields[11,12]

B.2 Totally aromatic 1H-pyrrolo[3,2-c]quinolines

As was mentioned in the introduction the first example of the system was all aromatic 1H-pyrrolo[3,2-c]quinoline (I) obtained from the chemical degradation of the indigo dye "Ciba yellow"[2]. The other derivatives of I were obtained in a different way as described below.

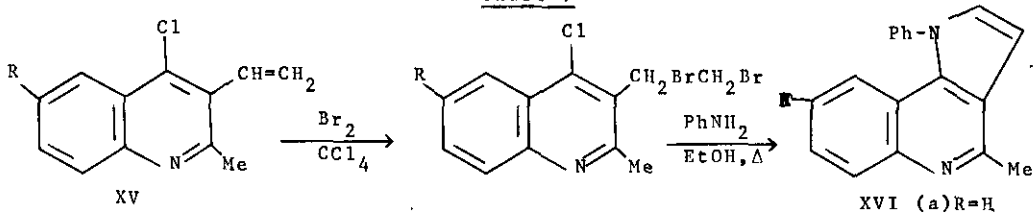
The dihydropyrrolo[3,2-c]quinoline (V) (chart 2) was dehydrogenated by refluxing with 10% palladium charcoal in diphenyl ether to give 1-phenyl-1H-pyrrolo[3,2-c]quinolin-4-one (XIV) (chart 6)[8]

chart 6



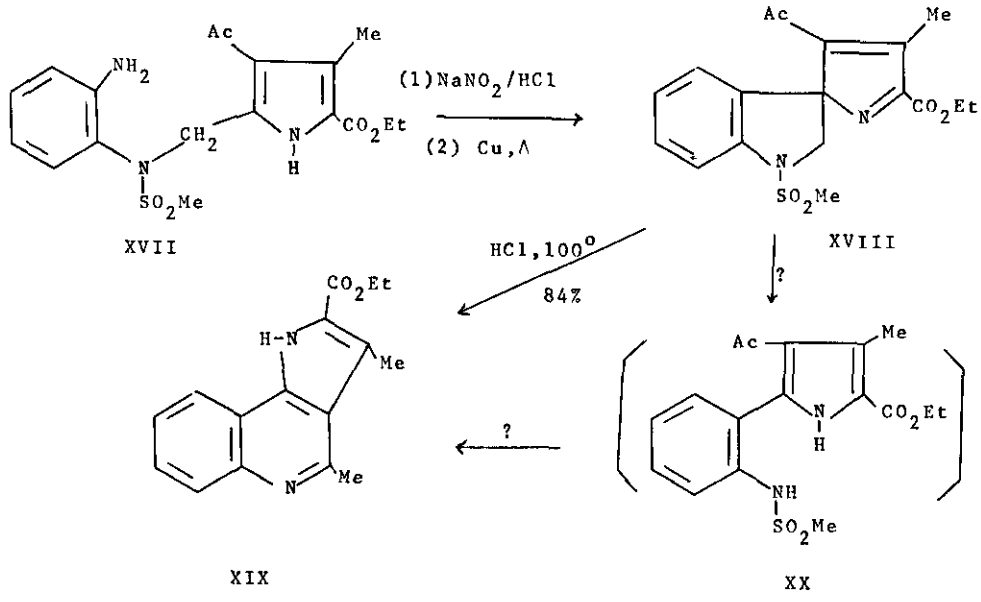
By a slight variation of the method used for the synthesis of dihydro-1H-pyrrolo[3,2-c]quinolines, Nagaoka prepared 4-methyl-1-phenyl-1H-pyrrolo[3,2-c]-quinoline (XVIa) in 77% yield and its 8-methoxy derivative (XVIb) from 4-chloro-3-vinylquinolines (XV) by the route presented in the chart 7[14].

chart 7



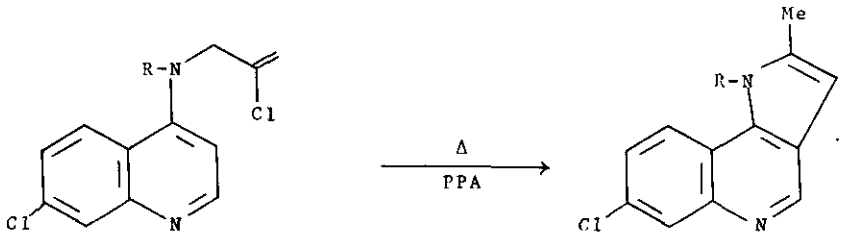
During the Pschorr cyclization studies of pyrrole derivatives, Beveridge and Huppatz[15] obtained a spiroindoline (XVIII) from the copper-catalyzed decomposition of the diazonium salt derived from XVII. The spiroindoline (XVIII) on treatment with concentrated hydrochloric acid gave 84% yield of ethyl 3,4-dimethyl-1H-pyrrolo[3,2-c]quinoline-2-carboxylate (XIX). The expected phenylpyrrole derivative (XX), though proposed as an intermediate in this reaction, was not isolated from this reaction. The reaction scheme is presented in chart 8.

chart 8



2-Chloroallylanilines have been found to be excellent intermediates in the synthesis of indoles and thus McDonald and Proctor[16] extended this reaction to the corresponding quinoline derivatives in order to varify its effectiveness in the synthesis of 1H-pyrrolo[3,2-c]quinolines. 7-Chloro-4-[N-(2-chloroallyl)ethylamino]quinoline (XXIa), prepared from 4,7-dichloroquinoline and N-(2-chloroallyl)-ethylamine, when treated with polyphosphoric acid at 90-94° gave 42% yield of 7-chloro-1-ethyl-2-methyl-1H-pyrrolo[3,2-c]quinoline (XXIIa). A similar reaction of XXIb gave XXIIb in 30% yield (chart 9).

chart 9

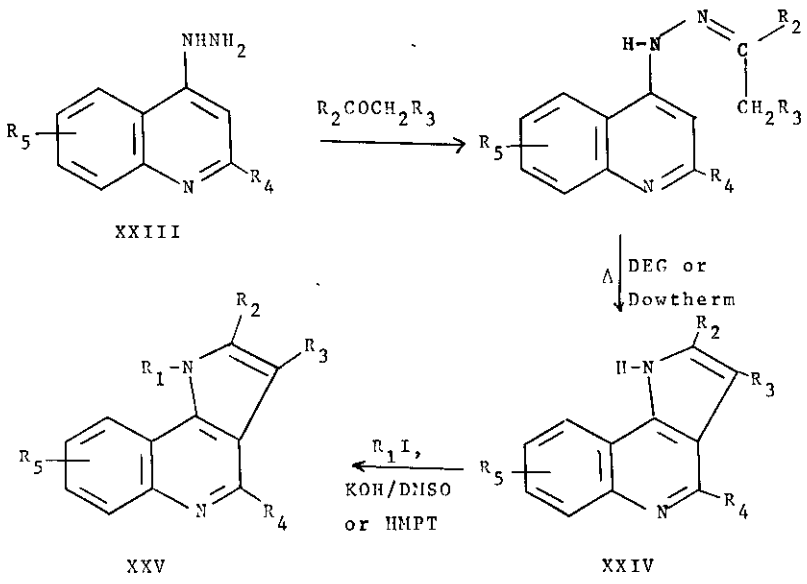


XXI (a) R= Et
(b) R=Ph

XXII (a) R=Et
(b) R=Ph

The Fischer "Indolization" method although an obvious choice for the synthesis of 1H-pyrrolo[3,2-c]quinolines from the corresponding 4-hydrazinoquinolines had in the past posed problems in the quinoline series due to the use of acid conditions for cyclizations of the hydrazones. This difficulty has only recently been overcome by effecting cyclizations of the quinolylhydrazones in high boiling solvents. Thus Parrick and Wilcox[17] synthesized 2,3-dimethyl-, 2,3-diphenyl-, and 2,3,4-trimethyl-1H-pyrrolo[3,2-c]quinolines in respective yields of 82, 70, and 82% by effecting cyclizations of the corresponding 4-quinolylhydrazones in diethylene glycol (DEG). Independantly Khan and Rocha[18,19] have also prepared a large number of 1H-pyrrolo[3,2-c]quinoline derivatives (XXIV) in excellent yields (generally over 60%) under thermal conditions of cyclizations in diethylene glycol or in dowtherm starting from the 4-hydrazinoquinolines (XXIII). The synthetic scheme for these cyclizations is presented in the chart 10.

chart 10



R_1=H, Me, Et; R_2=H, Me, Et; R_3=Me, Et, Ph; R_4=H, Me; R_5=H, 6-Cl, 7-Cl, 8-Cl, 6-Me, 7-Me, 8-Me, 6-OMe, 7-OMe, 8-OMe

C. REACTIONS

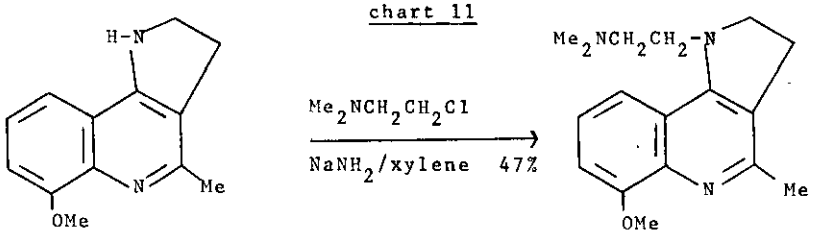
C.1 Salt formation

Both the reduced as well as totally aromatic 1H-pyrrolo[3,2-c]quinolines are capable of forming salts and in fact many derivatives of the system were isolated and characterized as hydrochlorides and hydrobromides[3,5,7-9]. Some other salts such as maleate or naphthalenedisulfonates have also been prepared[3].

C.2 N-alkylations

N-Alkylations of some reduced derivatives have been accomplished and lead to the formation of 1-alkyl , or 1-aralkyl derivatives as examplified for the N,N-dimethylaminoethylation of 2,3-dihydro-6-methoxy-4-methyl-1H-pyrrolo[3,2-c]-quinoline (chart 11)[3].

chart 11



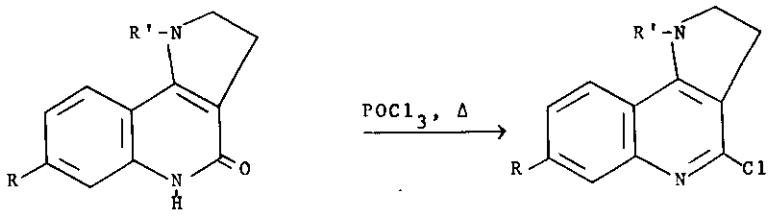
Some XXIV when alkylated with methyl or ethyl iodide gave ca. 90% yield of the corresponding N-alkylated 1H-pyrrolo[3,2-c]quinolines (XXV) (chart 10)[19].

C.3 Modification of substituent

Very few reactions for the modification of the substituents have been carried out. In some cases the substituent undergoing modification was not even on the parent ring system such as in the demethylation of 2,3-dihydro-1-methoxyphenyl-4-methyl-1H-pyrrolo[3,2-c]quinolines with hydrobromic acid[3,6].

A hydroxy group in the 4 position of pyrrolo[3,2-c]quinoline ring was converted into the chloro group by treatment with phosphoryl chloride and in this manner 4-chloro-1-phenyl-1H-pyrrolo[3,2-c]quinoline was obtained in 84% yield by refluxing XIV with phosphoryl chloride for one hour. A similar treatment of V led to the corresponding derivative XXVI[8] and of XXVII to the corresponding chloro derivative XXVIII[9] in the yields of 81 and 40% respectively (chart 12).

chart 12



R=H, R'=Ph (V)

R=Cl, R'=$PhCH_2$ (XXVII)

XXVI R=H, R'=Ph

XXVIII R=Cl, R'=$PhCH_2$

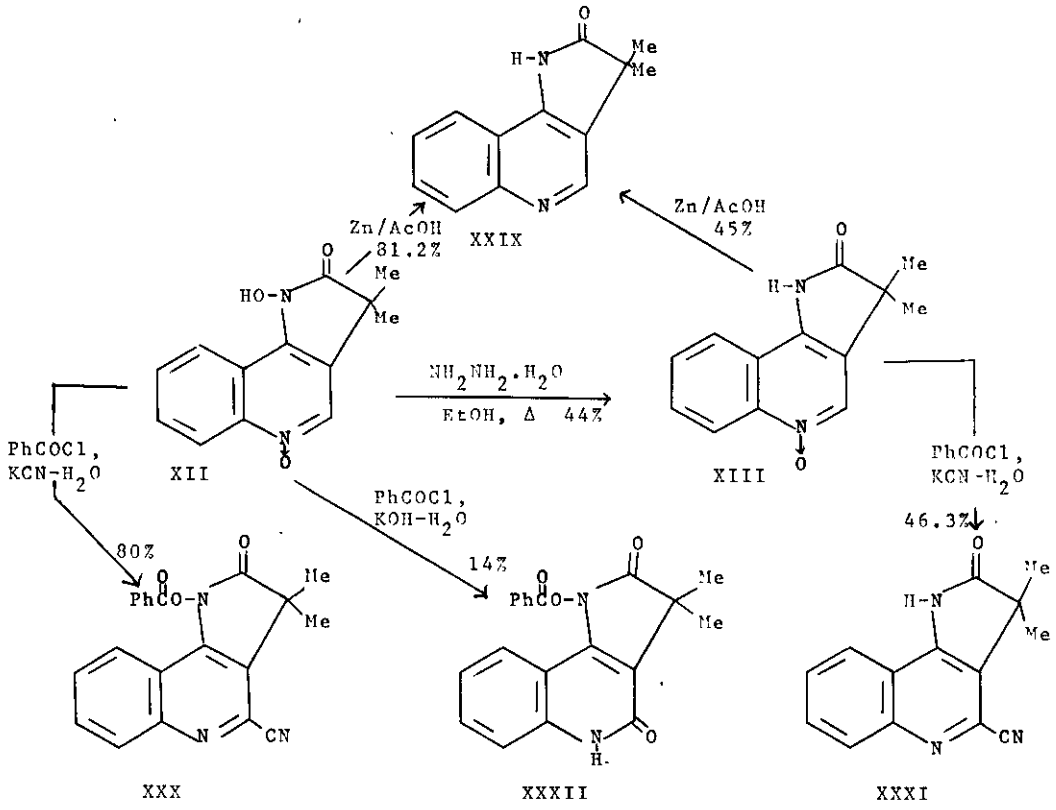
The chloro group introduced in the 4 position can also undergo other reactions. Thus the catalytic reduction of XXVI removes the chloro group[8], while the reaction of XXVIII with benzylamine gives VIIIa in 96.5% yield by a nucleophilic substituition[9].

The N-oxide function can be deoxygenated by reduction with zinc and acetic acid[12] or with phosphorous trichloride[10]. Thus on heating with phosphorous trichloride the N-oxide (XI) was deoxygenated in 53% yield[10].

The methyl group in the 4 position may be oxidized to the acid and the acid thus obtained could either be decarboxylated or be converted to the amides[4]. The decarboxylation of the 2,3-dicarboxylic acid has already been mentioned in connection with the first example of the system[2].

The product (XII) obtained from the reaction of 4-nitroquinoline 1-oxide with isobutyraldehyde enamines has been subjected to various reactions such as the reduction of N-hydroxy function, deoxygenation, Reissert reaction etc. These are outlined in chart 13[12]. The reduction of XII or XIII with zinc and acetic acid

chart 13



removes both the N-hydroxy as well as the N-oxide function to give XXIX while hydrazine preferentially reduces the N-hydroxy group of XII. The Reissert reactions of XII as well as of the XIII, like quinoline N-oxide[20], give the corresponding 4-cyano derivatives XXX and XXXI respectively with the concomitant formation of the N-benzoate in the case of XII. The treatment of XII with benzoyl chloride and aqueous potassium hydroxide gave 14% yield of 1-benzoyloxy-2,3-dihydro-3,3-dimethyl-1H-pyrrolo[3,2-c]quinolin-2,4-dione (XXXII).

D. SPECTRA

D.1 Ultraviolet spectra

The ultraviolet spectra of some of the derivatives of 1H-pyrrolo[3,2-c]-quinolines as reported in the literature are presented in the Table 1. The ultra-

violet spectrum of XIX showed an α-band system characteristic of polycyclic aromatic compounds. This information together with other spectral data helped in establishing its structure[15].

TABLE 1. ULTRAVIOLET SPECTRA OF PYRROLO[3,2-c]QUINOLINES

compd. no.	$\lambda_{max.}$ nm (log ε)	solvent	ref.
V	232(4.62), 268[§](3.96), 331(4.12).	-	8
VIIIb	230(4.64), 267(4.45), 340(4.05).	MeOH	9
XIV	238(4.80), 274(3.86), 284(3.84), 315(3.98), 328(4.05).	-	8
XIX*	267(4.63), 293[§](4.03), 310[§](3.92), 324(3.46), 340(3.20).	-	15

*approx.; measured from the published figure
§inflection

D.2 Proton magnetic resonance spectra

The proton magnetic resonance spectra of a number of derivatives of 1H-pyrrolo[3,2-c]quinoline (reduced as well as totally aromatic) have been reported in the literature[9,12,15-17,19] and were helpful in proving the structures of the cyclized products.

The proton magnetic resonance spectrum of the dihydro compound (VIIIb) measured in a mixture of deuterochloroform and trifluoroacetic acid shows two triplets at 3.24 and 4.12 ppm with a coupling constant of 9 Hz due to the protons at C-3 and C-2 respectively of the pyrrolidine ring of the molecule[9].

The totally aromatic 1H-pyrrolo[3,2-c]quinolines show all the usual signals due to the substituent groups as well as due to the protons of the benzene ring of the system (with the expected coupling constants)[15-17,19]. In the rest of the spectrum the proton due to a free NH gives a broad signal between 11.72 and 12.60 ppm and could easily be exchanged with deuterium[17,19]. The signal for the proton at C-2 appears between 7.05 and 7.40 ppm but at 6.77 ppm in the N-alkylated products[19]. The signal for the proton at C-3 appears between 6.77 and 6.93 ppm[16] and for the proton at C-4 as a downfield singlet between 8.72 and 9.18 ppm[16,17,19].

D.3 Infrared spectra

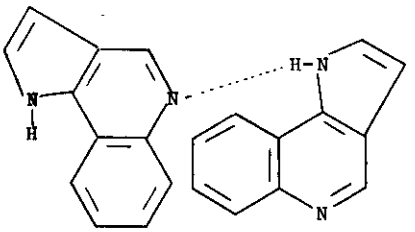
The infrared spectra of 1H-pyrrolo[3,2-c]quinolines were also of great help in assigning the structures of the reaction products and some of the most characteristic absorption bands are collected in Table 2.

TABLE 2. INFRARED SPECTRA OF 1H-PYRROLO[3,2-c]QUINOLINES

compd. no.	Infrared absorption cm^{-1}	ref.
V	1640(C=O) (KBr)	8
VIIIb	1620, 1590 sh., 1570 (nujol)	9
XI	1760(C=O), 1715(C=O)	10
XII	3640-2200 br.(OH), 1740(C=O) (KBr)	12
XIII	3700-2100 br,(NH), 1730(C=O) (KBr)	12
XIV	1650(C=O) (KBr)	8
XIX	3310(NH), 1662(C=O) (nujol)	15
XXVI.HCl	2421($\overset{+}{N}$H) (KBr)	8
XXIX	3600-2300 br.(NH), 1730(C=O) (KBr)	12
XXX	2225(C≡N), 1781(C=O), 1763(C=O) (nujol)	12
XXXI	3600-2600 br.(NH), 2245(C≡N),1725(C=O) (KBr)	12
XXXII	3200-2400 br.(NH), 1785(C=O), 1753(C=O), 1655(C=O) (KBr)	12

The intense infrared absorption bands at 1640 and 1650 cm^{-1},due to the 2-quinolone structure of V and XIV respectively, gave strong support in favour of the pyrrolo[3,2-c]quinoline rather than the furo[2,3-b]quinoline structure[8].

Numerous 1H-pyrrolo[3,2-c]quinolines synthesized by Khan and Rocha[19] showed a broad absorption band between 3500 and 2500 cm^{-1} due to an intermolecular hydrogen bonding as depicted in XXXIII. This absorption band totally disappears on N-alkylations.

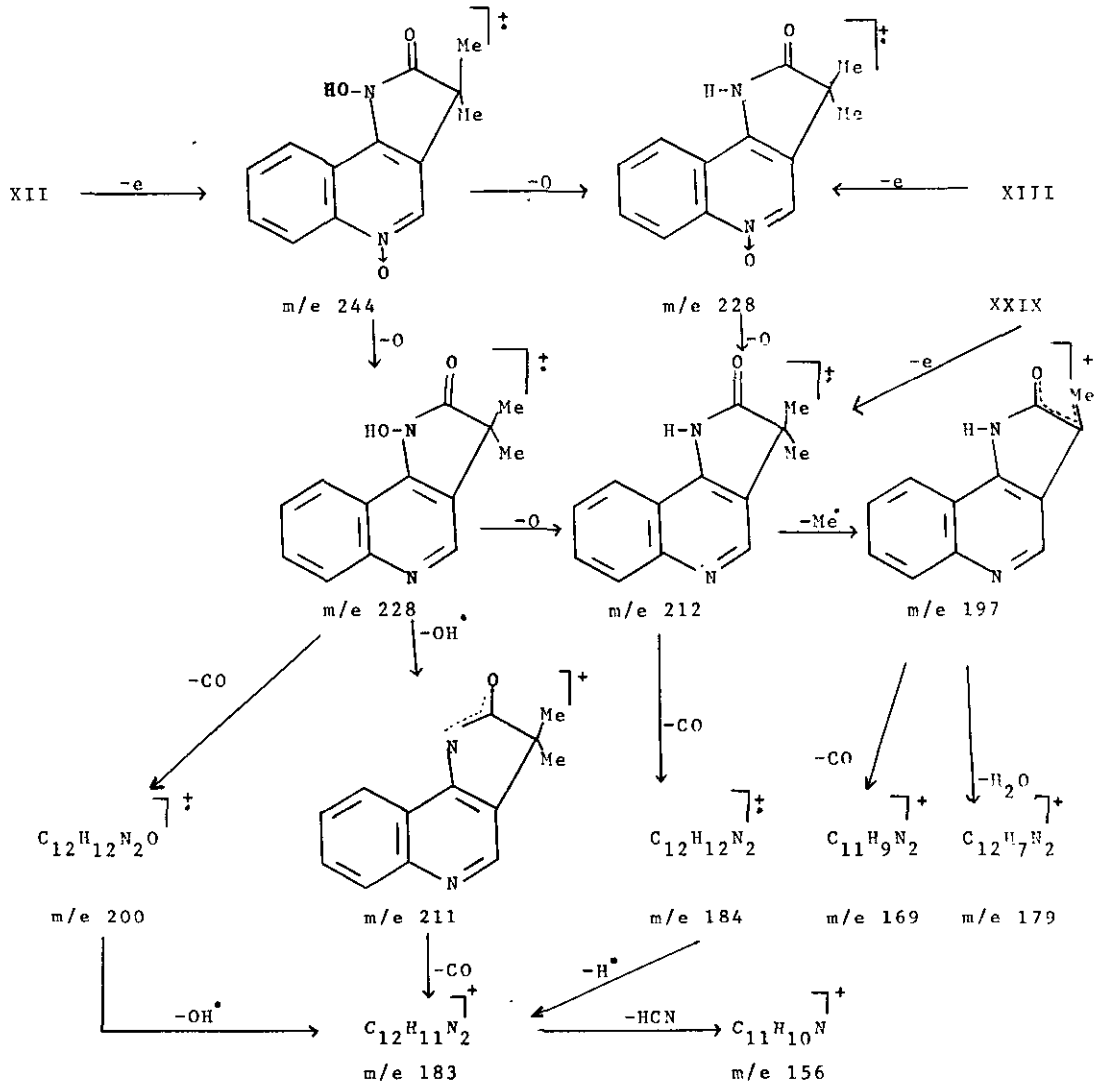


XXXIII

D.4 Mass spectra

The molecular ions observed in the mass spectra were of great help in establishing the structures of compounds XII and XIII[12], and of XIX[15]. A scheme showing the fragmentation patterns of XII, XIII and XXIX has also been suggested[12] and is presented in the chart 14. The first fragment peaks appear to be produced

chart 14



by elimination of an oxygen atom. This is followed by the elimination of other fragments such as CO, Me, H_2O, HCN etc.

E.BIOLOGICAL ACTIVITY

Very few 1H-pyrrolo[3,2-c]quinolines have undergone biological testing and of those tested were found to be useful as antimalarials[5], amebicides[3], and as hypotensive agents[7].

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