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

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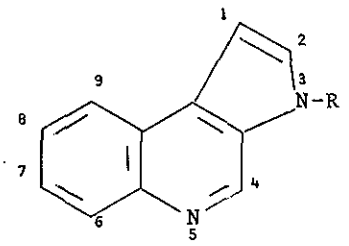
A review of the chemistry of 3H-pyrrolo[2,3-c]-quinoline ring system is presented. It includes the synthesis and reactions together with the recorded spectral data of some of the derivatives.

CONTENTS

A. INTRODUCTION

The ring system pyrrolo[2,3-c]quinoline (I) generated interest during the structure elucidation of the alkaloid calycanthine. The chemical degradation of the alkaloid had resulted in the formation of a base $C_{12}H_{10}N_2$ which was thought to be a pyrroloquinoline and to establish the identity of this base a number of similar pyrroloquinolines , including 3-methyl-3H-pyrrolo[2,3-c]quinoline (II), were synthesized. It was found that II was identical (m.p., mixed m.p., and ultraviolet spectrum) with the base isolated from the chemical degradation of calycanthine[2]. Some other derivatives of I were also obtained from the degradation of another alkaloid echitamine[3,4].



I R=H

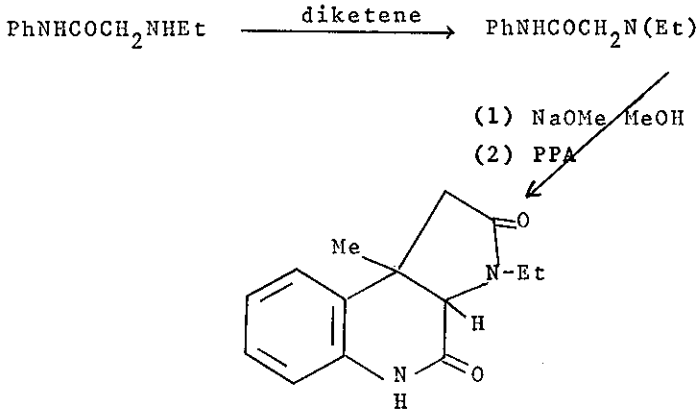
II R=Me

B. SYNTHESES

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

The reaction of derivatives of α-amino acids with diketene followed by treatment with a base gives a pyrrole derivative but in one case cis 3-ethyl-3,3a,5,9b-tetrahydro-1H-pyrrolo[2,3-c]-quinolin-2,4-dione (III) was also obtained as the main product of

chart 1



III

of the reaction (chart 1)[5].

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

Starting from 3-nitrolepidine, the first aromatic 3H-pyrrolo-[2,3-c]quinoline was obtained by Eiter and Nagy whose synthetic scheme is outlined in chart 2. The reduction of the nitrolepidine afforded 3-aminolepidine which was converted into its N-formyl derivative by reaction with formic acid. The 3-formamidolepidine was cyclized by heating it with phosphorous pentoxide in vacuum at 250-260° to give the parent ring system I. The methylation of I with methyl iodide produced the N-methyl derivative II[2].

Fischer's indolization method has also been applied for the synthesis of 3H-pyrrolo[2,3-c]quinolines. In one procedure 2-phenyl-3-quinolylhydrazine was transformed into the corresponding hydrazones of carbonyl compounds and the cyclization was affected by heating with concentrated hydrochloric acid on a steam

chart 2

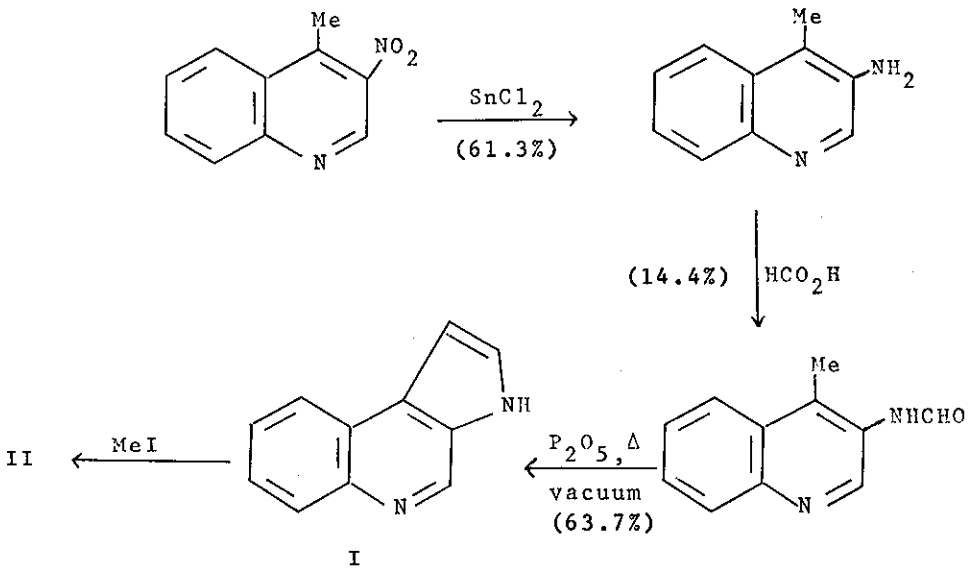
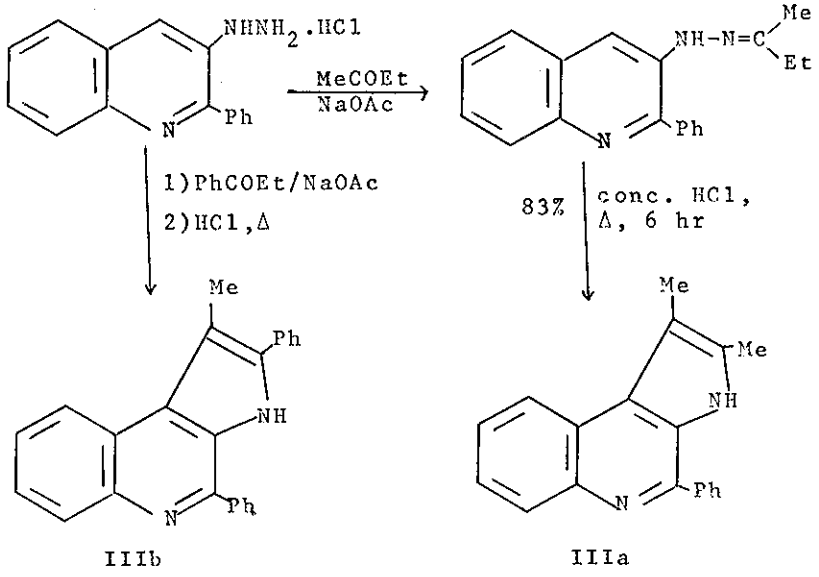


chart 3

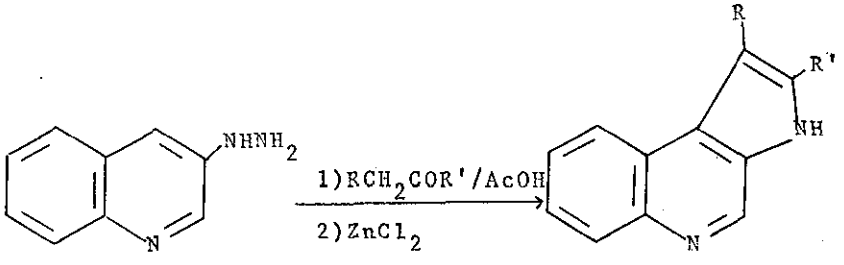


IIIb IIIa

bath for a period of six hours and the pyrroloquinoline IIIa was isolated as the hydrochloride. In a similar manner IIIb was obtained in an unspecified yield when the reaction was carried out with propiophenone (chart 3)[6].

On the other hand Govindachari et al.,[7] in their synthesis of 3H-pyrrolo[2,3-c]quinolines, used zinc chloride at 260° or zinc chloride in p-cymene under reflux to affect cyclization of various 3-quinolylhydrazones in yields ranging from 6 to 77% (chart 4).

chart 4



IV R= H ; R'= Me (9%)

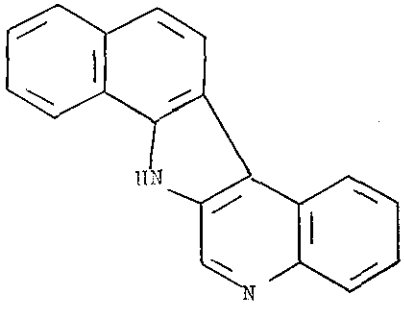
V R= R'= Me (6%)

VI R= Me; R'=Et (44%)

VII R= H; R'= Ph (42%)

VIII R=Me; R'=Ph (24%)

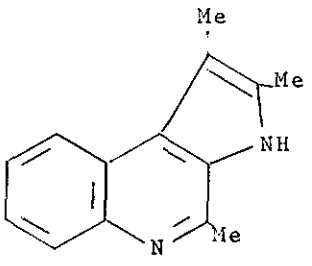
IX R= R'=Ph (77%)



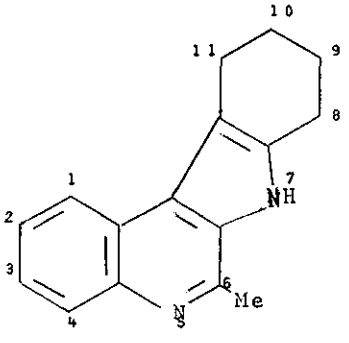
XI

During their cyclization of ethyl pyruvate 3-quinolylhydrazone the ester group was hydrolyzed and the acid thus formed decarboxylated to give 3H-pyrrolo[2,3-c]quinoline (I) in 9.4% overall yield. The I thus obtained was found to be identical with the I previously synthesized by Eiter and Nagy[2]. Under the similar reaction conditions α-tetralone 3-quinolylhydrazone gave 26% yield of 12,13-dihydro-1,2:6,7-dibenzo-β-carboline (X) which was dehydrogenated over palladium on charcoal to give dibenzo-β-carboline XI.

More recently Parrick and Wilcox obtained 1,2,4-trimethyl-3H-pyrrolo[2,3-c]quinoline (XII) and 6-methyl-8,9,10,11-tetrahydro-7H-indolo[2,3-c]quinoline (XIII) in respective yields of 70 and 75% by cyclizing butanone 2-methyl-3-quinolylhydrazone and cyclohexanone 2-methyl-3-quinolylhydrazone respectively in refluxing diethylene glycol. No acid catalyst was used in these cyclizations. This method was also applied by these workers to affect similar cyclizations of other quinolylhydrazones[8].



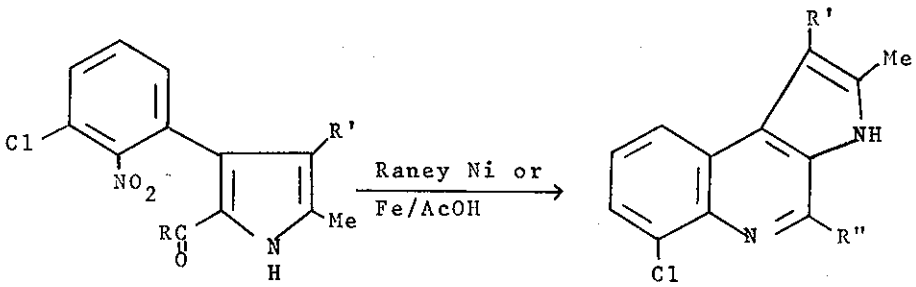
XII



XIII

In a different approach pyrrole-2-carboxaldehyde or ethyl pyrrole-2-carboxylate containing o-nitroaryl substituent in the 3 position was used for the synthesis of 3H-pyrrolo[2,3-c]quinolines. Thus the reduction of 4-chloro-5-methyl-3-(2'-nitro-3'-chlorophenyl)pyrrole-2-carboxaldehyde (XIVa) with Raney nickel catalyst gave 64% yield of XV[9] while the reduction of ethyl 5-methyl-3-(2'-nitro-3'-chlorophenyl)pyrrole-2-carboxylate (XIVb) with iron-acetic acid gave XVI in 80% yield[10] (chart 5).

chart 5



XIVa R=H, R'=Cl

XIVb R=OEt, R'=H

XV R'=Cl, R"=H

XVI R'=H, R"=OH

Comparing the synthetic methods, not withstanding the particular requirements, Fischer's indolization method as adapted by Parrick and Wilcox[8] (use of diethylene glycol as solvent for thermocyclization) seems to be the method of choice for the synthesis of a variety of 3H-pyrrolo[2,3-c]quinolines from the relatively simple and easily available starting materials. On the other hand the method using substituted pyrroles (chart 5) is limited by the availability of not so simple starting material.

C.REACTIONS

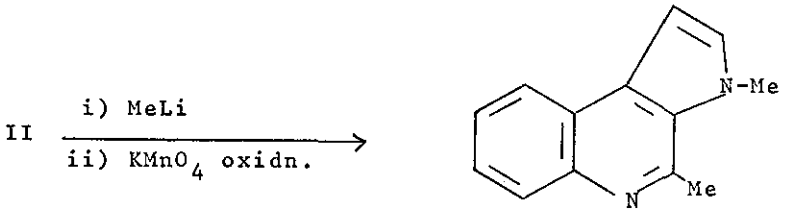
C.1 N-Alkylation

The first alkylation reaction of the parent ring system was carried out during the structure elucidation of calycanthine. The alkylation of I with methyl iodide resulted in the formation of 3-methyl-3H-pyrrolo[2,3-c]quinoline which was identical with the base $C_{12}H_{10}N_2$ obtained from the degradation of the alkaloid[2] (see chart 2).

C.2 C-Alkylation

The compound II on treatment with methyllithium followed by permanganate oxidation led to the formation of 3,4-dimethyl-3H-pyrrolo[2,3-c]quinoline (XVII) (chart 6). The compound XVII was isolated as its picrate and was identical with the compound obtained on zinc dust distillation of the tertiary base isolated from the alkaloid echitamine[3].

chart 6



XVII

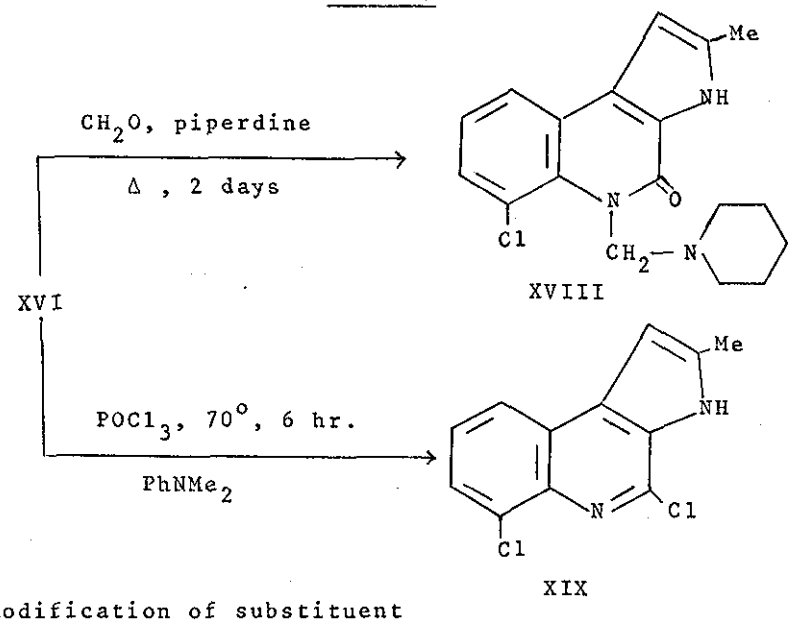
C.3 N-Acylation

Atkinson and Mattocks[6] attempted N-acylation of IIIa with acetyl chloride and with acetic anhydride but without success.

C.4 Mannich reaction

The Mannich reaction of XVI with formaldehyde and piperidine gave XVIII in 49% yield (chart 7)[11].

chart 7



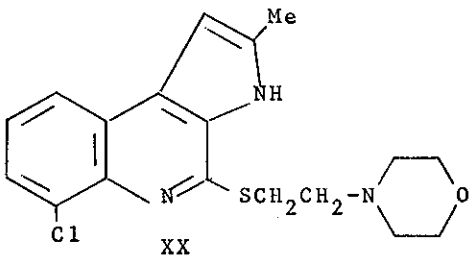
C.5 Modification of substituent

There were very few reactions that were carried out to modify the substituents. When XVI was treated with phosphoryl chloride there resulted 63% yield of 4,6-dichloro-2-methyl-3H-pyrrolo-[2,3-c]quinoline (XIX) (chart 7)[12].

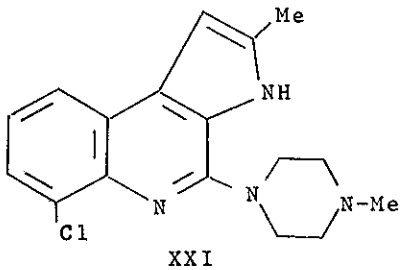
6-Chloro-2-methyl-3H-pyrrolo[2,3-c]quinoline-4(5H)-thione when reacted with 4-(2'-chloroethyl)morpholine in the presence of sodium gave 7% yield of 6-chloro-2-methyl-4-[(2'-morpholinoethyl)-thio]-3H-pyrrolo[2,3-c]quinoline (XX)[13].

In another substituent modification reaction when XIX was refluxed in xylene with N-methylpiperazine there resulted

6-chloro-2-methyl-4-(4'-methylpiperazin-1'-yl)-3H-pyrrolo[2,3-c]-quinoline (XXI) in a yield of 24%[14].



XX



XXI

D.SPECTRA

D.1 Ultraviolet spectra

The only recorded ultraviolet spectra of 3H-pyrrolo[2,3-c]-quinolines are presented in table 1. The simple pyrroloquinolines were reported to exhibit a characteristic violet fluorescence in acid solution while the 2-phenyl derivatives (VII-IX) exhibit a blue fluorescence even in neutral solution. The compounds I, II, IV and X show, in acid solutions, a bathochromic shift of 20-30 nm of their longest wavelength bands[7].

D.2 Proton magnetic resonance spectra

Only the proton magnetic resonance spectra of XII and XIII (in DMSO-d_6) are reported in the literature[8]. The proton magnetic resonance spectrum of XII showed the following signals: δ 2.2 (9H,s,3xMe), 7.3 (2H,m,7- and 8-H), 8.1 (1H,m,9-H), 8.2 (1H,m,6-H), and 11.5 (1H,s,NH,disappeared on addition of D_2O), and for XIII: δ 1.8 (3H,s,Me), 3.3 (8H,s,4xCH_2), 7.3 (2H,s,2- and 3-H), 7.7 (1H,m,1-H), 8.4 (1H,m,4-H), and 11.7 (1H,s,NH,disappeared on addition of D_2O).

D.3 Infrared spectra

Once again there is not much information about the infrared

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

compd. No.	$\lambda_{max.}$ nm (logε)	Ref.
I	240(4.47), 305(4.03), and 320*(3.91).	7
I§	230(4.37) and 342(4.03).	7
II+	245 and 307.	4
II§	265, 327, and 355.	4
IV	230(4.54), 245(4.56), 312(4.21), and 325(4.18).	7
IV§	262*(3.66), 275(3.46), and 345(4.25).	7
V	230(4.38), 240(4.39), and 325(4.09).	7
VI	230(4.49), 240*(4.48), and 325(4.18).	7
VII	235(4.52), 260(4.36), and 335(4.52).	7
VIII	235(4.39), 255(4.35), and 335(4.29).	7
IX	240*(4.43), 260(4.43), and 335(4.44).	7
X	240(4.45), 265(4.25), 350(4.46), and 368(4.38).	7
X§	235(4.46), 260(4.29),350(4.03), and 395(4.42).	7
XI	245(4.31), 275(4.66), 300(4.31), 355(4.29), 380*(3.75), and 405*(3.40).	7

*inflection

§in acid solution

+in ethanol

spectra of 3H-pyrrolo[2,3-c]quinolines. Only a few absorption bands of a handful of compounds are reported. For example for II: 1385 cm^{-1}(?)[4], for XII: 3410 cm^{-1}(NH)[8]; and for XIII: 3445 cm^{-1} (NH)[8].

E. BIOLOGICAL ACTIVITY

A very few derivatives of 3H-pyrrolo[2,3-c]quinolines have been tested for biological activity. Those tested act as sedatives[10] or as central nervous system depressants[10-14].

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