PYRROLOQUINOLINES III[1]. PYRROLO[3,4-b]QUINOLINES

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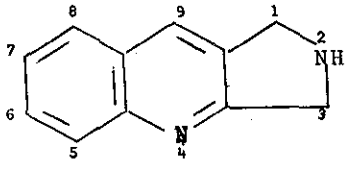
In the present review various routes for the synthesis of the pyrrolo[3,4-b]quinoline system, its reactions, and the spectral data for some of the derivatives of this system are presented.

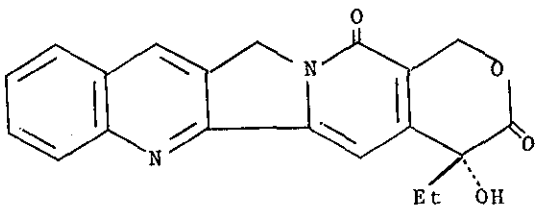
CONTENTS

A. INTRODUCTION

In 1916 von Niementowski and Suchardi[2] reported the first derivative of 2*H*-pyrrolo[3,4-*b*]quinoline ring system (I). This ring system forms part of the alkaloid camptothecin (II), isolated from the stem wood of Camptotheca acuminata and earlier it was claimed to have antileukemic and antitumor activity[3]. A good deal of interest in this ring system stems from the possibility of using appropriate derivatives of I for the synthesis of camptothecin or its analogs.



I



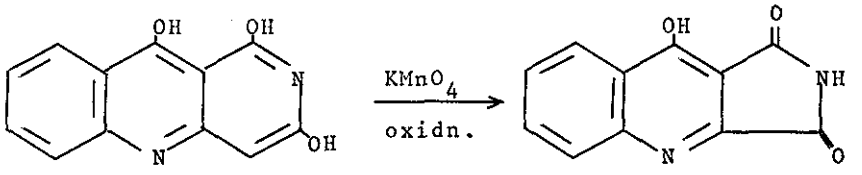
II

B. SYNTHESES

The first derivative of pyrrolo[3,4-*b*]quinoline was obtained

from the permanganate oxidation of 1,3,10-trihydroxybenzo-2,5-naphthyridine[2] (chart 1). The various syntheses of pyrrolo[3,4-b]-

chart 1

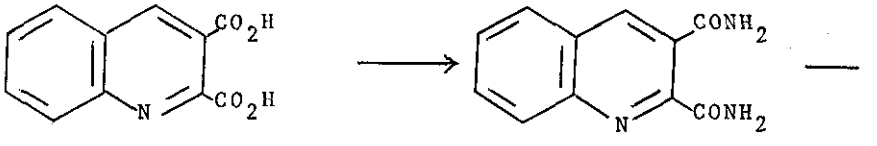


quinolines could be grouped according to the starting materials these syntheses employ and are described in the following:

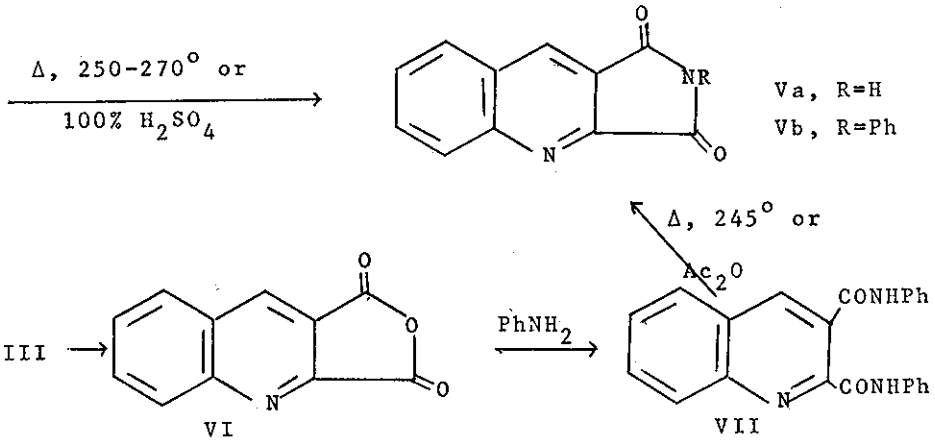
B.1 From quinolines

Various syntheses involving quinolines as starting materials use appropriately 2,3-disubstituted quinolines. Quinoline-2,3-dicarboxylic acid (III) was converted to its amide (IV) which on heating at 250-270° or treatment with 100% sulfuric acid gave 1,3-dihydro-2H-pyrrolo[3,4-b]quinolin-1,3-dione (Va). Whereas first conversion to the anhydride (VI) followed by treatment with aniline led to the dianilide (VII) which on heating at 245° or on treatment with acetic anhydride at 120° ring closed to yield 1,3-dihydro-2-phenyl-2H-pyrrolo[3,4-b]quinolin-1,3-dione (Vb)[4] (chart 2). In an

chart 2



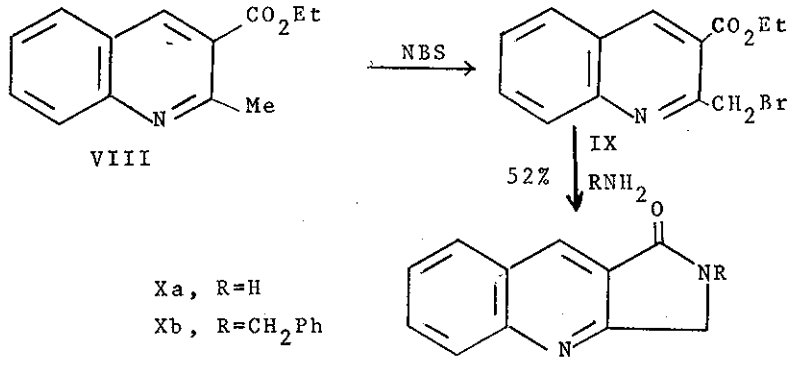
III IV



alternative procedure III was directly converted, in 70% yield, to Va by heating with a mixture of acetamide and acetic anhydride[5]. Aminolysis of the anhydride VI by various other aromatic and heterocyclic amines also gave other N-derivatives of V[6].

Bromination of ethyl 2-methylquinoline-3-carboxylate (VIII) gives ethyl 2-bromoethylquinoline-3-carboxylate (IX) which on treatment with ammonia and with benzylamine afforded 2,3-dihydro-2H-pyrrolo[3,4-b]quinolin-1-ones, Xa and Xb (chart 3)[7].

chart 3



Sugasawa et al.[8] synthesized Xa from the quinoline diester (XI) through the sequence shown in chart 4. The same workers synthesized the isomeric 1,2-dihydro-3H-pyrrolo[3,4-b]quinolin-3-one (XVa) by the acid hydrolysis of the Reissert complex (XIV) formed by the reaction of potassium cyanide and benzoyl chloride on 3-acetamidoquinoline (XIII) (chart 5).

chart 4

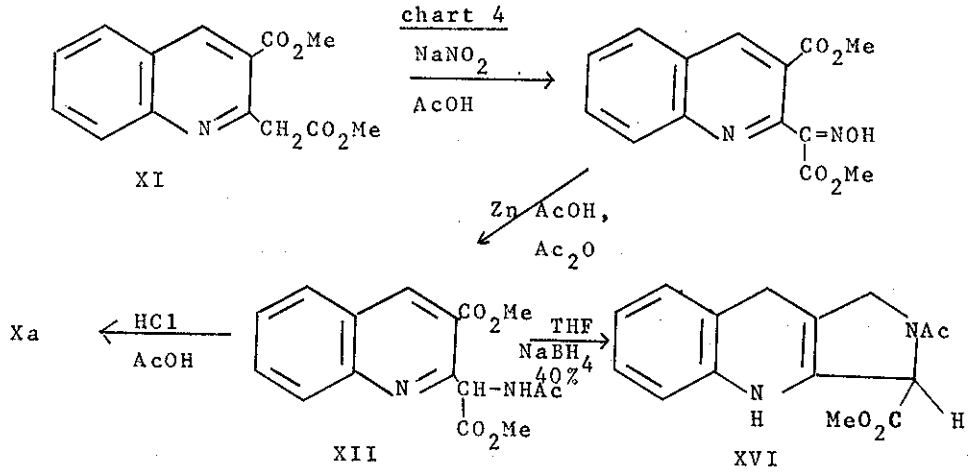
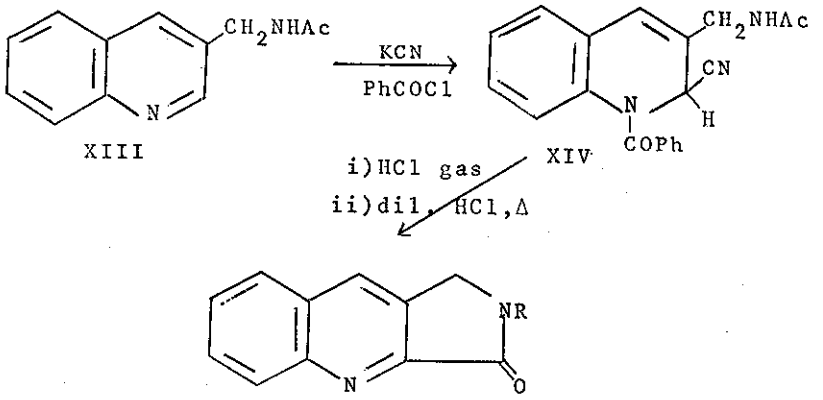


chart 5

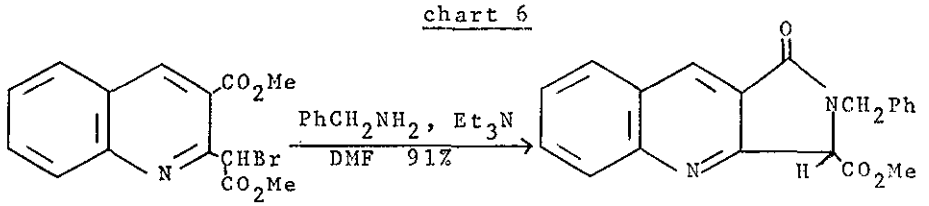


XVa R=H

XVb R=Me

During other attempts at the synthesis of pyrrolo[3,4-b]quinoline, when XII was treated with sodium borohydride, ring closure took place with simultaneous reduction of the pyridine ring to give XVI (chart 4), whereas the bromo derivative (XVII) of XI on treatment with benzylamine ring closed to afford XVIII in 91% yield (see chart 6)[9].

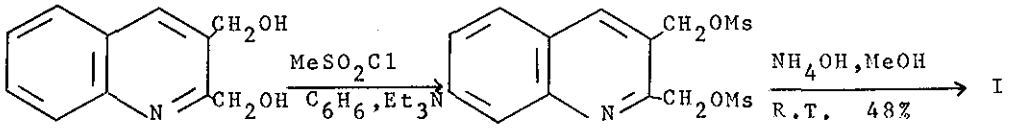
chart 6



XVII XVIII

Recently Corey and co-workers[10] synthesized 1,3-dihydro-2H-pyrrolo[3,4-b]quinoline (I) from 2,3-di(hydroxymethyl)quinoline by successive mesylation and amonolysis (chart 7). On the other hand Danishefsky and co-workers[11] employed methyl 3-methylquinoline-2-

chart 7

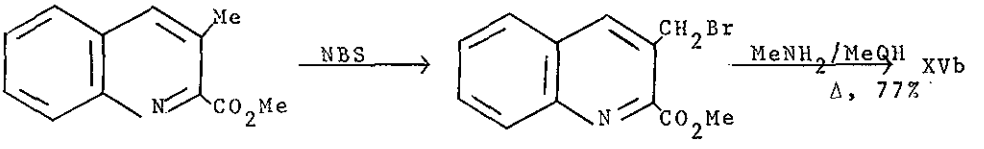


carboxylate (see chart 12 p.10 for the synthesis of this ester) for the synthesis of 1,2-dihydro-2-methyl-3H-pyrrolo[3,4-b]quinolin-3-one (XVb). Their synthetic scheme is outlined in the chart 8.

B.2 From o-aminobenzaldehydes and o-aminoaromatic ketones

During the synthetic studies of pyrrolo[3,4-b]quinolines ample use has been made of the Friedländer's method for the synthesis of quinolines. As we shall see both the acid and the base catalyzed

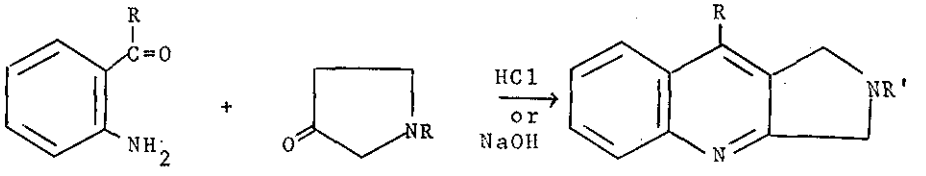
chart 8



ring closures were effected.

The condensation of o-aminobenzaldehyde (XIXa) with N-methylpyrrolidin-3-one (XXa) under base-catalyzed conditions led to the formation of XXIa whereas condensation of o-aminoacetophenone (XIXb) with XXa under acid conditions gave the product XXIb (see chart 9)[12]. The acid-catalyzed condensation of XIXa with XXb gave

chart 9

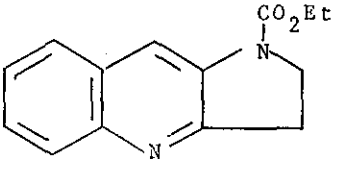


XIXa R=H
XIXb R=Me

XXa R'=Me
XXb R'=CO_2Et
XXc R'=Ac

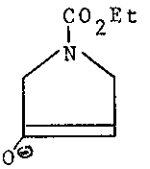
XXIa R=H;R'=Me (51%)
XXIb R=R'=Me (56%)
XXIc R=H;R'=CO_2Et
XXId R=H;R'=Ac

the expected XXIc together with 1-carbethoxy-2,3-dihydro-1H-pyrrolo[3,2-b]quinoline (XXII)[13].

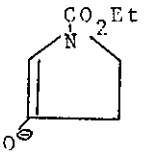


XXII

The preferential formation of XXIc under acid-catalyzed reaction of XIXa with XXb was also observed by Zalkow et al. who explained this selectivity as due to the increased stability of the enol corresponding to the structure A as well as the role played



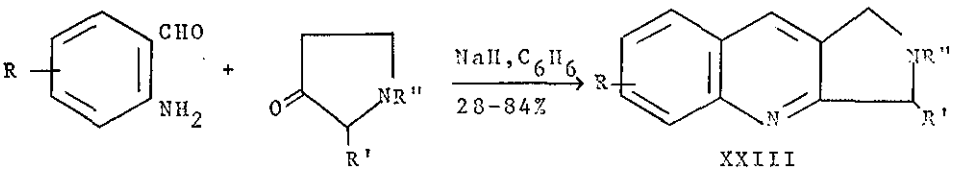
A



B

by the solvent. In the presence of acetic acid (which would lower the energy of the enol corresponding to B) equal amounts of XXI and XXII were formed while in its absence XXIc was formed in 88% yield. During this work Zalkow et al. obtained various others 1,3-dihydro-2H-pyrrolo[3,4-b]quinolines (I; XXIc;XXId; and 7-chloro-, 7-methoxy-, 8-methoxy-, and 7,8-methylenedioxy- derivatives of XXIc) in yields ranging from 13 to 31%[14]. Using substituted o-aminobenzaldehydes as well as substituted pyrrolidin-3-one, various derivatives of I (XXIII) had been obtained (chart 10)[15-17]. In another

chart 10



XXIII

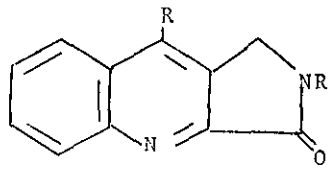
R=H, OMe, etc.

R'=H, CH_2CO_2Et, CH_2CO_2H, etc.

R"=CO_2Et, CH_2Ph, etc.

procedure a Schiff's base of o-aminobenzaldehyde with p-tolualdehyde was condensed with a pyrrolidin-3-one in the presence of p-toluenesulfonic acid in toluene to afford XXIII (R=H, R'=CH_2CO_2Et, R"=CO_2Et) in 76.3% yield[18].

Using acid catalysis (a mixture of acetic acid and sulfuric acid) in the condensation of pyrrolidin-2,3-dione with o-aminoacetophenone or o-aminobenzophenone and base catalysis (potassium hydroxide) in the condensation with isatin, Madhav and Southwick were able to prepare XXIV in excellent yields (71% to quantitative yields)[19]. Reductive ring closures of o-nitrobenzylidene derivatives of pyrrolidin-2,3-dione with tin(II) chloride gave XXIV (R=H, R'=cyclohexyl; 44.2% yield) and XXIV (R=H, R'=phenethyl; 51.4% yield) while reduction with sodium dithionite gave a low yield (16.6%) of XXIV (R=H, R'=cyclohexyl)[20].



R=H, Ph, Me, CO_2H

R'= cyclohexyl, CH_2Ph

XXIV

Some Friedländer-type condensations leading first to appropriately substituted quinolines were also carried out. These quinolines reacted further to give pyrrolo[3,4-b]quinolines. These are presented in the charts 11-13. 2-Methyl-1,3-diphenyl-2H-pyrrolo-[3,4-b]quinoline (XXV), obtained in one of these syntheses (chart 13) is the only known example of the totally aromatic system[23].

chart 11[21]

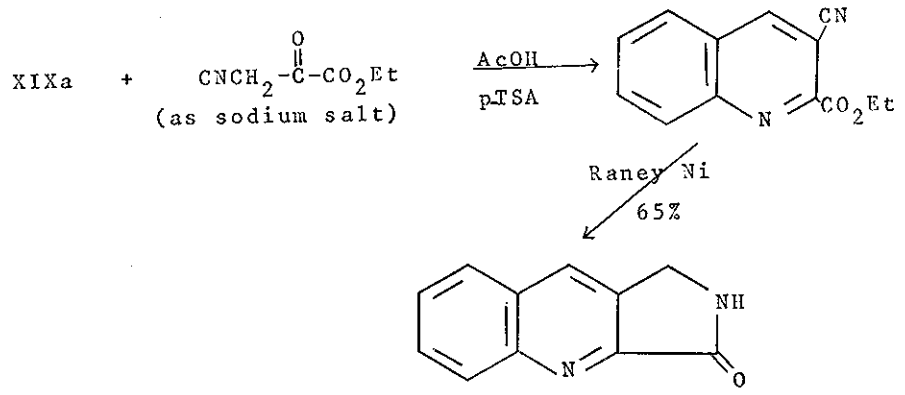


chart 12[22]

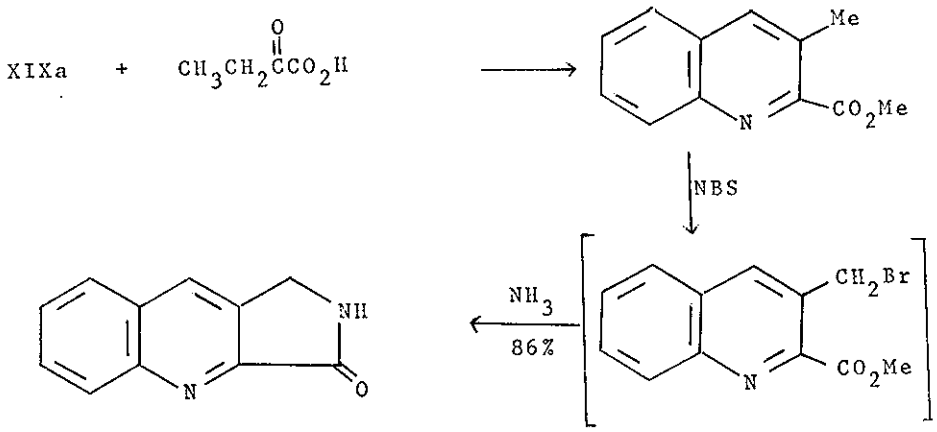
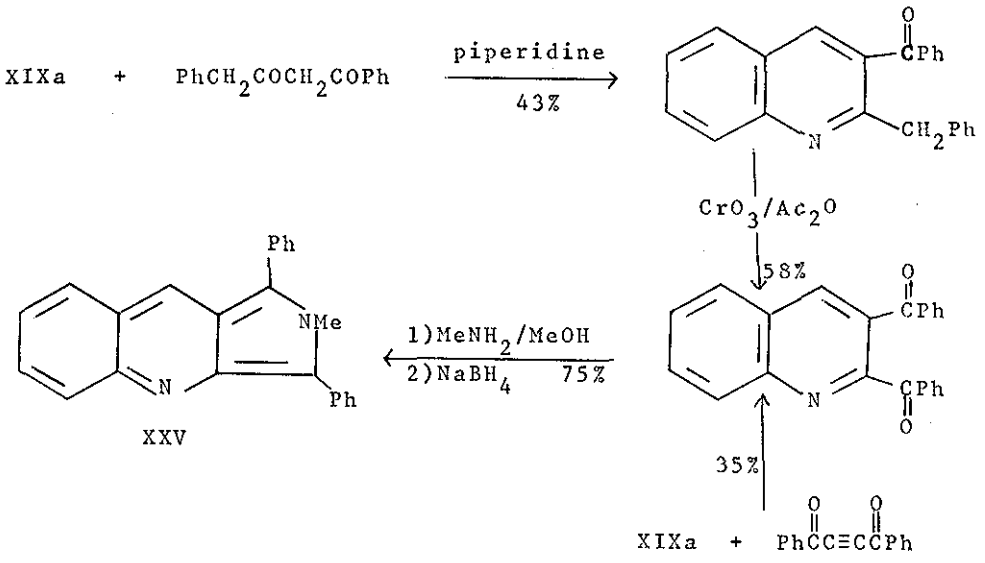


chart 13[23]

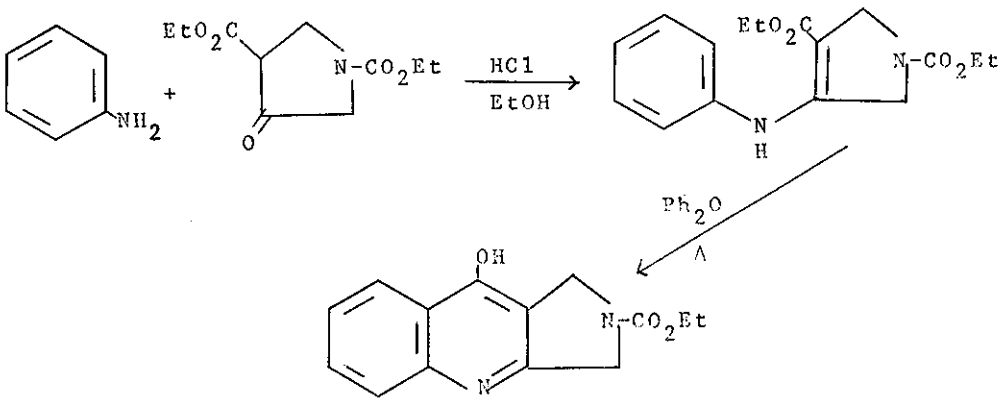


B.3 From β-ketoesters

In addition to the synthetic routes described above, synthesis of the pyrrolo[3,4-b]quinoline system has been accomplished by using appropriate β-ketoesters in Conrad-Limpach-type synthesis.

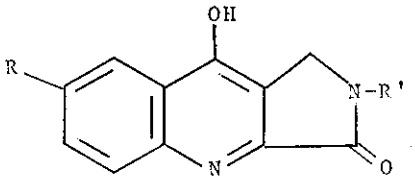
Thus aniline was allowed to condense with 1,4-dicarbethoxy-pyrrolidin-3-one in ethanol containing hydrochloric acid and the resulting intermediate was thermally cyclized in diphenyl ether to 2-carbethoxy-9-hydroxy-2H-pyrrolo[3,4-b]quinoline (XXVI)[16] (see chart 14). Tanaka et al.[7] used the same scheme for the synthesis of XXVI with the only difference that they used calcium sulfate in acetic acid in the condensation step instead of using hydrochloric acid. On the other hand Madhav, Dufresne, and Southwick made use

chart 14



XXVI

of formic acid for the condensation of appropriately substituted anilines and ethyl pyrrolidin-3-one-4-carboxylates and obtained, after cyclization in diphenyl ether, some 1,2-dihydro-3H-pyrrolo-[3,4-b]quinolines (XXVII) in yields ranging from 57.3 to 80.3%[24].



XXVII

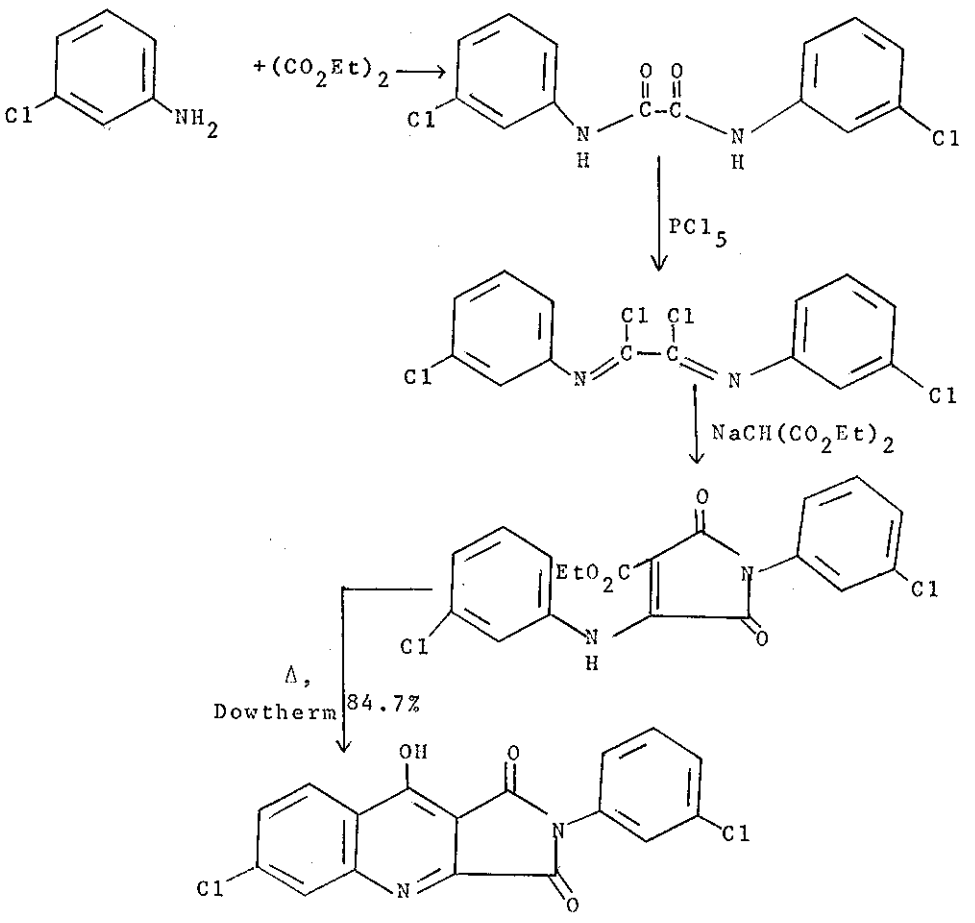
R=H, Cl, OMe

R'=cyclohexyl or Ac

B.4 Miscellaneous

There are a few isolated examples of pyrrolo[3,4-b]quinolines obtained by other methods. Price and Velzen[25] obtained a by-product

chart 15

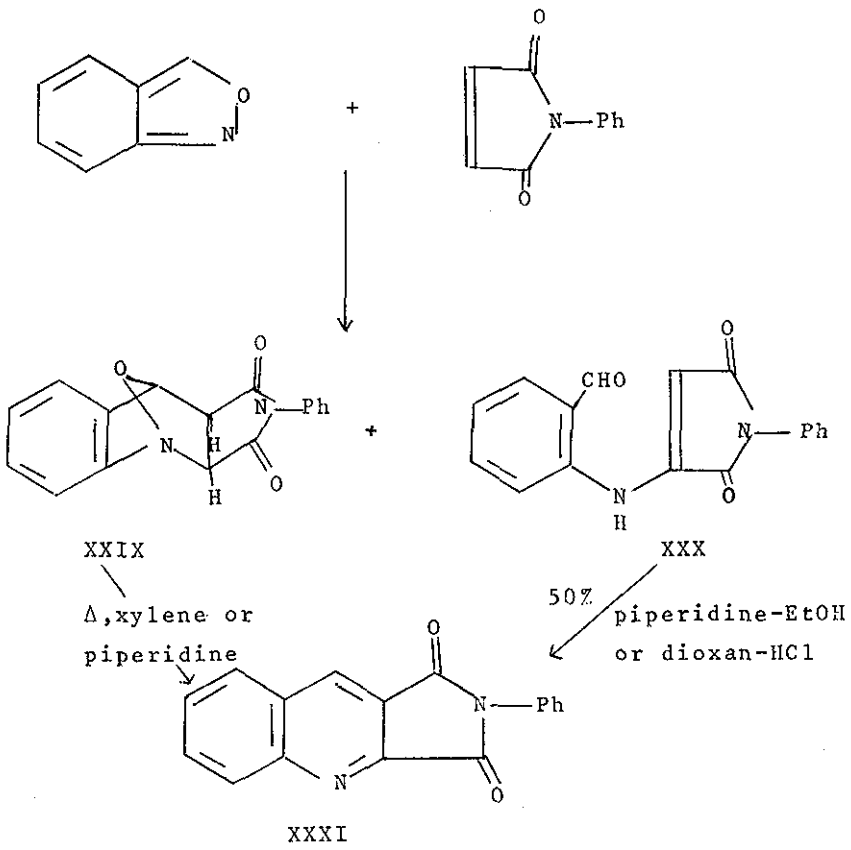


XXVIII

from a reaction of oxanilide of m-chloroaniline with phosphorous pentachloride followed by a condensation with sodio diethylmalonate. This by-product on heating under reflux in Dowtherm cyclized to give the pyrrolo[3,4-b]quinoline (XXVIII). The reaction scheme is outlined in the chart 15 above.

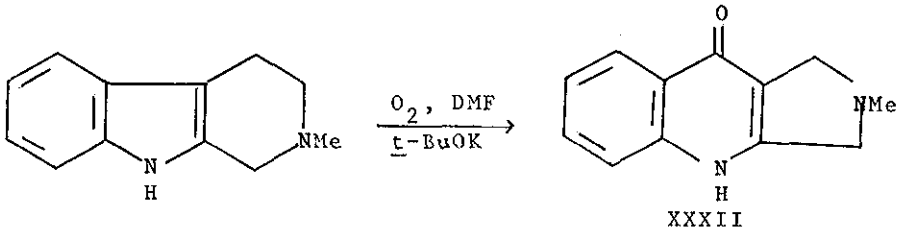
A *Diels-Alder reaction* of N-phenylmaleimide with anthranil gave an exo adduct (XXIX) and 2-formylanilino-N'-phenylmaleimide (XXX). When XXIX was heated for twenty hours in refluxing xylene, 1,3-dihydro-2-phenyl-2H-pyrrolo[3,4-b]quinolin-1,3-dione (XXXI) was obtained. The pyrroloquinoline XXXI could also be obtained from either XXIX or XXX by treating it with an ethanolic solution containing a small amount of piperidine, or with dioxan containing hydrochloric acid[26] (chart 16).

chart 16



Some pyrrolo[3,4-b]quinoline derivatives e.g. XXXII have also been obtained, in good yields, from the β-carboline derivatives by oxidation in the presence of potassium t-butoxide[27] (chart 17).

chart 17



XXXII

C. REACTIONS

C.1 Salt formation

With the acids I forms salts which are more stable than the free base. The dihdrobromide of I can be stored indefinitely without decomposition and from which I can be easily recovered on treatment with triethylamine[14]. The I and some of its derivatives have been obtained as dihydrochlorides[7,35,36].

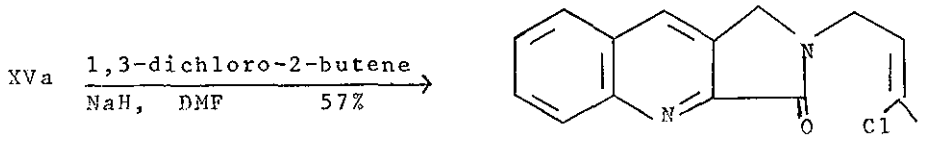
C.2 N-Alkylations

Although various N-acylations have been performed on the pyrrolo[3,4-b]quinoline system (see below), there is only one example of N-alkylation. Thus Danishefsky and co-workers[11], using sodium hydride in N,N-dimethylformamide, alkylated XVa with 1,3-dichloro-2-butene to obtain XXXIII (chart 18).

C.3 N-Acylations

Most of the N-acylations on I or its derivatives were performed to produce suitable precursors for the synthesis of camptothecin. Various acylating agents (simple as well as complex

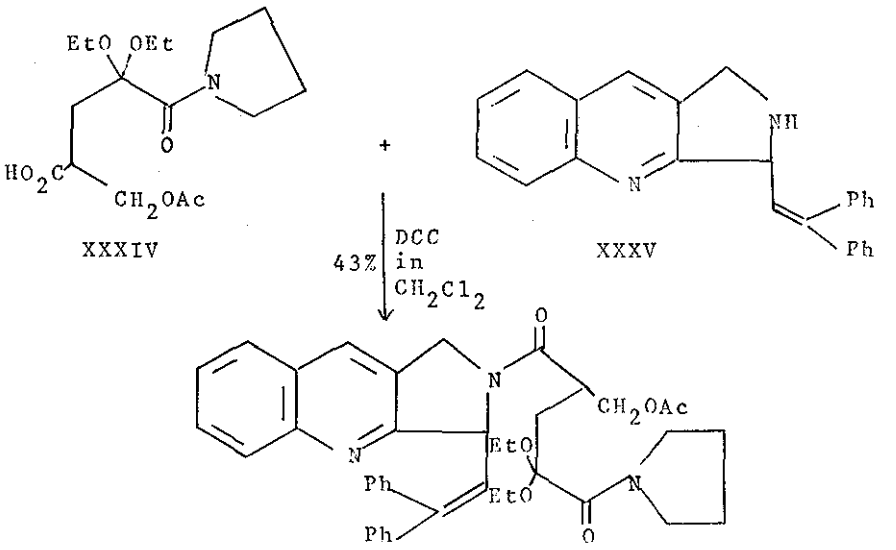
chart 18



XXXIII

compounds) and a variety of conditions were employed to effect these acylations. For example 5-acetoxy-4-carboxy-2,2-diethoxy-pentanoic acid pyrrolidine amide (XXXIV) was condensed with 1,3-dihydro-3-(2',2'-diphenylvinyl)-2H-pyrrolo[3,4-b]quinoline (XXXV) in dichloromethane using dicyclohexylcarbodiimide (DCC) to form XXXVI[17] (chart 19).

chart 19



XXXVI

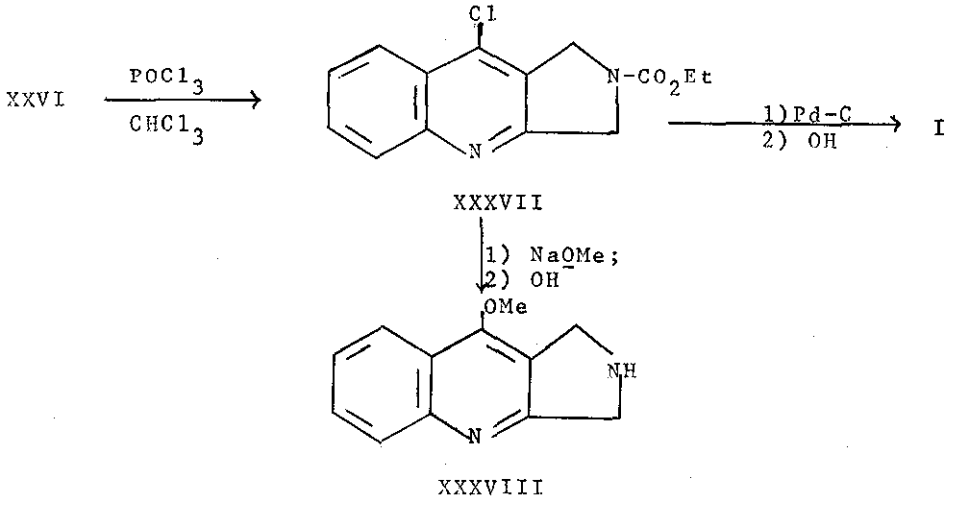
While dicyclohexylcarbodiimide was used by some workers to bring about N-acylations[7,29,30,33], others carried out N-acylations using sodium carbonate[28], thallous oxide[21], pyridine[10], or by simply heating the pyrrolo[3,4-b]quinolines with an ester or an acid[21,22,31,32,34].

C.4 Modification of substituent

The ethyl pyrrolo[3,4-b]quinoline-1-carboxylates obtained in some syntheses were hydrolyzed either by alkaline hydrolysis[7,14,35,36], or by heating with hydrobromic acid[14] or hydriodic acid[18]. In all these cases hydrolysis is accompanied by decarboxylation of the resulting acid.

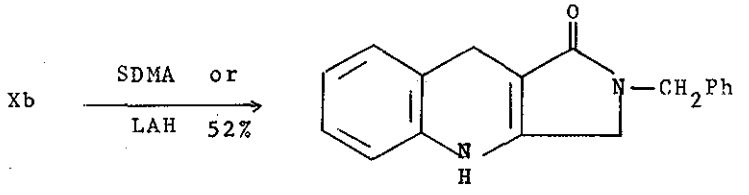
The hydroxy group in the nine position of XXVI has been converted into the chloro group by reaction with phosphoryl chloride to give XXXVII, the chloro group of which was in turn replaced by the methoxy group on treatment with sodium methoxide to give XXXVIII[7,37] (chart 20).

chart 20



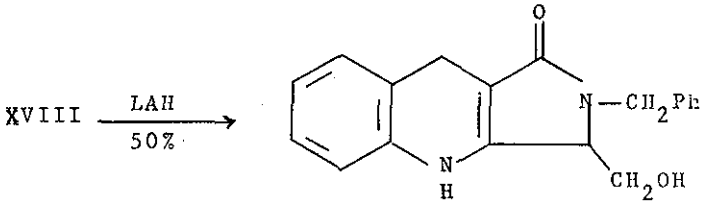
The catalytic reduction of XXXVII followed by hydrolysis led to I[7] (chart 20). The reduction of Xa with lithium aluminum hydride failed to give I but instead of Xa when Xb was reduced under these conditions the product obtained was XXXIX in which the pyridine ring was reduced. The same product was obtained in the reduction of Xb by sodium bis-(2-methoxyethoxy)aluminum hydride (SDMA) (chart 21). The compound XXXIX is susceptable to aerial oxidation and reverts back to Xb during crystallization[7].

chart 21



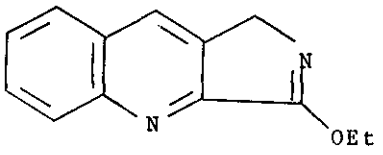
XXXIX

In a similar manner the reduction of XVIII with lithium aluminum hydride failed to produce a product in which the amide carbonyl group was reduced but instead XL was obtained where once again the pyridine ring was reduced in addition to the ester group[9].



XL

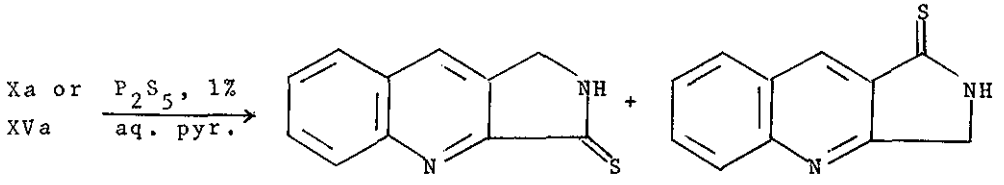
Meerwein reagent(triethyloxonium fluoroborate) converts XVa to 3-ethoxy-1H-pyrrolo[3,4-b]quinoline (XLI) which was utilized in the synthesis of d,l-camptothecin[21]. The yield of XLI was 52%.



XLI

The reaction of XVa with phosphorous pentasulfide gave a mixture of XLII and XLIII. The same mixture of the two products was obtained in the reaction of phosphorous pentasulfide with Xa[8,38] (chart 22). The compound XLII could not be converted to

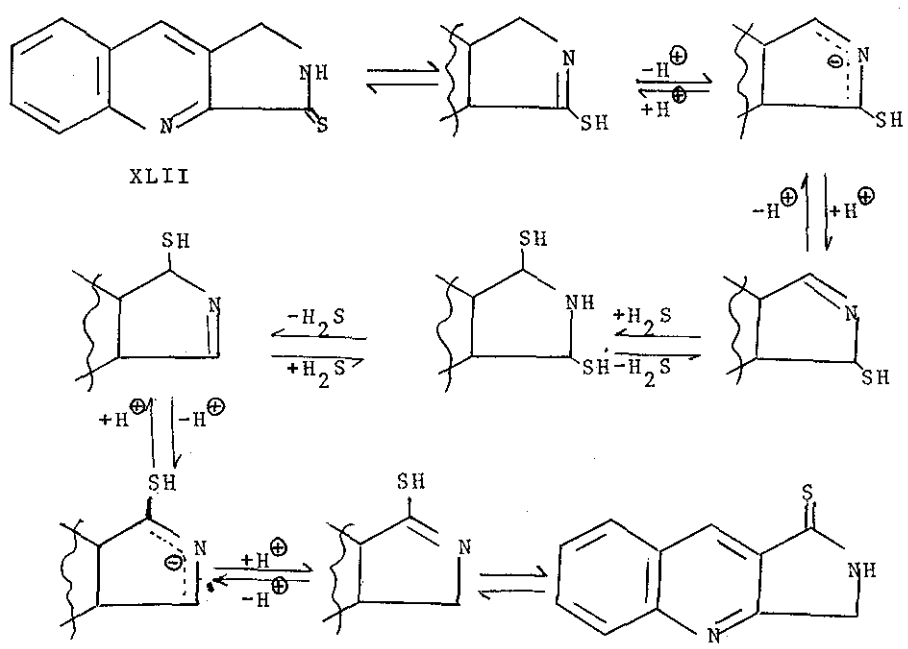
chart 22



XLII (12%) XLIII (73%)

XLIII by simple heating whereas the presence of phosphorous pentasulfide or hydrogen sulfide facilitated this conversion. Based on these observations Sugasawa et al.[8] concluded that the compound XLIII is more stable than XLII and that the sulfur atom at C-3 in XLII did not shift directly to C-1 in XLIII but rather another molecule of phosphorous pentasulfide or hydrogen sulfide attacked at C-1 in XLII followed by elimination of the sulfur atom at C-3 to give XLIII and this involves an equilibrium between base-catalyzed deprotonation and protonation together with the addition and elimination of hydrogen sulfide. Their proposed mechanistic scheme is presented in the chart 23 below.

chart 23



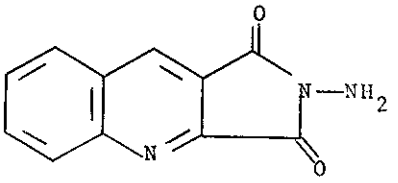
XLII

XLIII

C.5 Other reactions

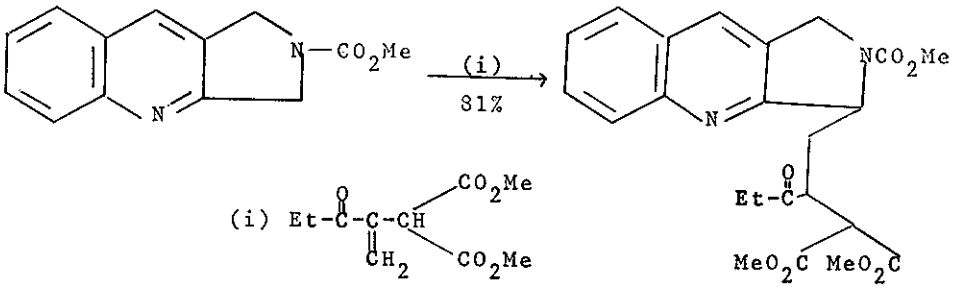
The 3 position of appropriately substituted 2H-pyrrolo[3,4-b]-quinolines can participate in the Michael condensation reaction. An example of this reaction is shown in chart 24[28]. The reaction proceeds without any catalyst. Still in different schemes for the synthesis of camptothecin suitable reaction conditions were used to effect condensation at this position of 2H-pyrrolo[3,4-b]quinolines with other reagents[10,30,32-34]. (see for example charts 26&27).

The reaction of hydrazine with Va led to the formation of an N-amino derivative XLIV[39]



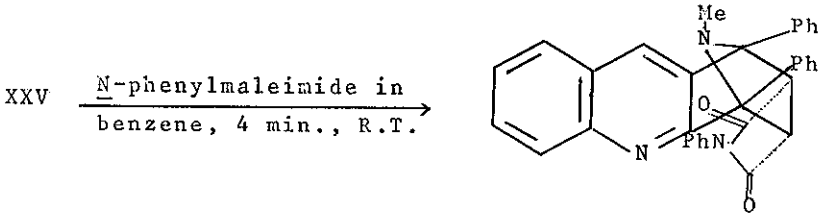
XLIV

chart 24



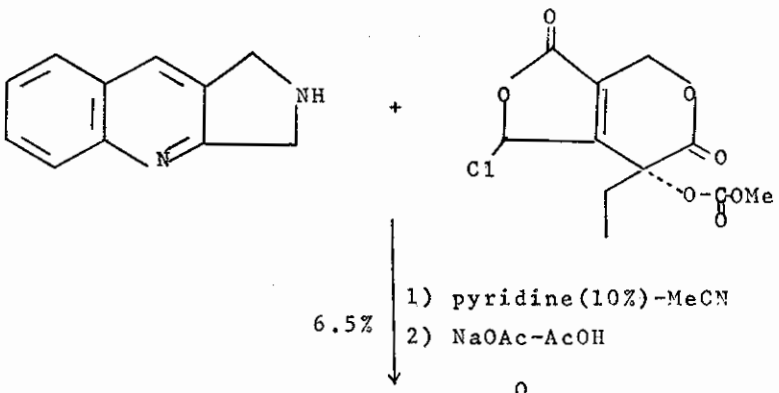
Totally aromatic 2-methyl-1,3-diphenyl-2H-pyrrolo[3,4-b]quinoline (XXV) behaves as a diene and on reaction with N-phenylmaleimide gives the endo adduct XLV (chart 25), which reverts to the starting material before melting[2 3]

chart 25



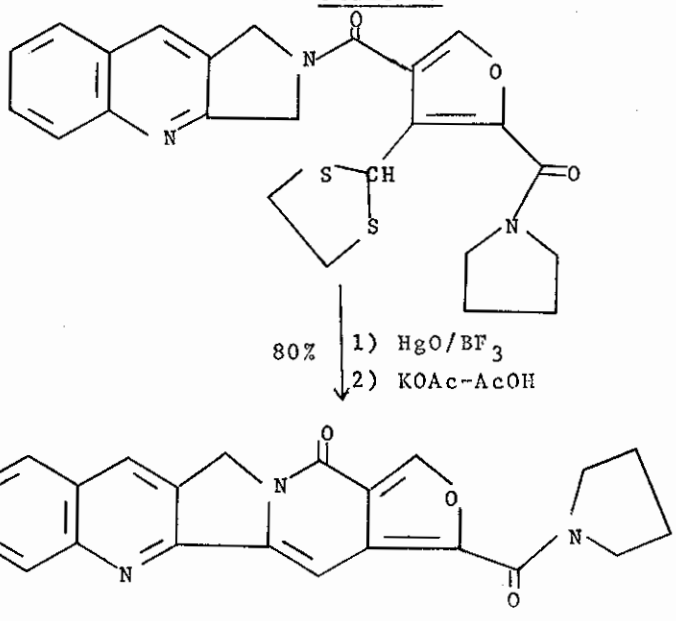
XLV

chart 26[10]



II

chart 27[30]



D. SPECTRA

D.1 Ultraviolet spectra

The ultraviolet spectra of 2H-pyrrolo[3,4-b]quinolines XXIa and XXIb display absorption bands between 319-321, 284-287, and 234-237 nm and could be compared with 2,3-cycliclepidine which has absorption bands at 320-321, 280-286, and 231-233 nm[12]. In a similar manner the ultraviolet spectra of some XXVII were compared with 2,3-cyclopentenoquinolone to establish the identity of the predominant tautomeric form but was found not to be much useful for this purpose[24]. Although the ultraviolet spectra of a host of other derivatives of I are reported in the literature[7,10,11,14,15,17,26,31-33, and 39], here we have chosen to list in the Table 1 the ultraviolet spectra of some of these derivatives.

D.2 Proton magnetic resonance spectra

The proton magnetic resonance spectra of many derivatives of I, majority of these being intermediates in the synthesis of camptothecin or its analogs, have been reported in the literature (ref.[7-9,11,14,15,17-24, and 32-34]) and a few of these are listed in the Table 2. In the spectrum of XXV, N-methyl protons at δ4.08 are deshielded as compared to those of 1,3-diphenyl-2-methylisoindole (δ3.75). This deshielding is ascribed as due to the electron withdrawing effect of the nitrogen atom in the adjacent six-membered ring[23]

D.3 Infrared spectra

The infrared spectra of various pyrrolo[3,4-b]quinolines have been recorded[7-9,11,14,15,17-24,32-34, and 39]) and of these some are collected in the Table 3. In most of the cases these spectra

were used for diagnostic purpose. In no case a full analysis of the infrared spectrum was attempted.

TABLE 1. ULTRAVIOLET SPECTRA OF PYRROLO[3,4-b]QUINOLINES

compd. no.	$\lambda_{max.}$ nm (log ε)	solvent	ref.
XXIc	207(4.37), 229(4.16), 293(3.72), 299(3.85), 305 & 312(3.80).	MeOH	14
XXXI	221(4.03), and 261(4.25).	EtOH	26
XXXV	235, 265, 297, 307, 313, and 320.	EtOH	17
XXXVI	229(4.71), 256(4.30), 295(3.74), 302(3.69), 308(3.79), 314(3.74), and 323(3.93).	EtOH	17
XLIV	258 and 292	EtOH	39

TABLE 2. PROTON MAGNETIC RESONANCE SPECTRA OF PYRROLO[3,4-b]QUINOLINES

compd. no.	δ (ppm)	solvent	ref.
I	2.70(1H,s), 4.29(4H,s), and 7.30-8.10(5H,m).	$CDCl_3$	14
Xa	4.67(2H,s,$C\underline{H}_2$).	DMSO-d_6	8
XVa	4.69(2H,broad s,$C\underline{H}_2$).	DMF-d_7	8
XVb	3.47(3H,s), 5.00(2H,s), 8.00-8.30(4H,m), and 9.98(1H,s).	$CDCl_3$-CF_3CO_2H	11
XVIII	3.71(3H,s), 4.37 and 5.44(2H,AB quartet, J_{AB}=15Hz), 5.23(1H,s,C-3 $\underline{H}$), 7.32(5H,s), and ca. 7.50-8.50(5H).	$CDCl_3$	9

contd.

XXV	4.08(3H,s) and 7.30-7.70(15H,m).	$CDCl_3$	23
XXXIII	2.16(3H,s), 4.30-4.70(4H,m), 5.60-5.80(1H,m), 7.30-8.50(5H,m).	$CDCl_3$	11
XXXV	5.10(1H,d,J=9Hz,C-3 H), 5.60(1H,s,NH), and 6.18(1H,d,J=9Hz,olefinic H).	$CDCl_3$	17
XXXIX	3.88(2H,s), 4.07(2H,s), 4.75(2H,s), and 6.84-7.90(9H,m).	DMSO-d_6	
XL	3.64(2H,s,C-9 H_2), ca. 3.60-3.90(3H), 4.19 and 4.95(2H,ABquartet,J=16Hz), 4.91(1H,t, C-3 H), and 6.50-7.20(4H,arom.).	DMSO-d_6	9
XLI	1.53(3H,t,J=7Hz), 4.65(2H,q,J=7Hz), and 4.72(2H,s).	$CDCl_3$	21
XLII	5.08(2H,broad s,CH_2N), and 11.30(1H,broad NH).	DMF-d_7	8
XLIII	4.91(2H,s,CH_2N), and 11.10(1H,broad NH).	DMF-d_7	8

TABLE 3. INFRARED SPECTRA OF PYRROLO[3,4-b]QUINOLINES

compd. no.	infrared absorption cm^{-1}	ref.
I	3200(NH), 1640, and 1570 (KBr)	32
I	3250(NH), 1660, and 1553 (KBr)	14
Xa	3190,3185(NH), 1723, and 1705(C=O) (nujol)	8
XVa	3207, 3096(NH), and 1695(C=O) (nujol)	8
XVb	1704(C=O) ($CHCl_3$)	11
XVI	3223, 3120(NH), 3050, 1770, 1679, 1652(C=O), and 1540 (nujol)	9

contd.

XVIII	1745 and 1688(C=O) (nujol)	9
XXIc	1700, 1625, and 1570 (KBr)	14
XXV	1600, 1480, 1450, 1280, 1220, 760, and 750 (KBr)	23
XXXIII	1686 and 1667 (nujol)	11
XXXVI	1740(ester C=O), and 1640(amide C=O) (KBr)	17
XXXIX	3170 and 1675 (nujol)	7
XL	3300, 3190, 1665 sh., and 1638 (nujol)	9
XLI	1618, 1603, and 1580 ($CHCl_3$)	21
XLII	3110(NH), 1540, and 1530(C=S) (nujol)	8
XLIII	3123(NH), 1528(C=S) (nujol)	8
XLIV	3300, 3250, 3180, 3060, 3020, 1795, 1725, 1630, 1620, 1595, 1515, 1475, 1410, 1390, 1355, 1325, 1315, 1215, 1185, 1165, 1120, 1115, 1100, 1045, 1030, 990, 970, 945, 920, and 900 (KBr)	39

D.4 Mass spectra

As regards the mass spectra, the only information available is the molecular ions recorded in the literature[7-9,11,14,17,21,32,33]

E.BIOLOGICAL ACTIVITY

Some of the pyrrolo[3,4-b]quinolines have been found to be useful as herbicides[38] while others have been tested as drugs acting on circulatory system[29,35,37], and as analgesics[36].

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