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PYRROLOQUINOLINES I. 1H-PYRROLO[2,3-b]QUINOLINES

Misbahul Ain Khan* and João Ferreira da Rocha

Seção de Quimica, Instituto Militar de Engenharia,

Urca, Rio de Janeiro, RJ, Brasil

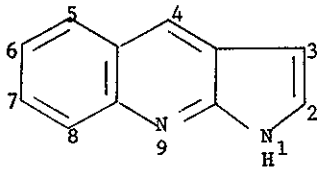
This article surveys the chemistry of 1H-pyrrolo-[2,3-b]quinoline including various synthetic routes employed for the preparation of its derivatves, their spectra and some of their properties.

CONTENTS

A. INTRODUCTION

The interest in the system pyrroloquinoline started during the

investigations of the constituents of the harmala alkaloids. In connection with the constitution of harmine and harmaline Perkin and Robinson attempted a synthesis of 1H-pyrrolo[2,3-b]quinoline (I) naming the parent all aromatic system as norisoharman and its 2-methyl derivative as isoharman[1]. The system I has its oxa analog - furo[2,3-b]quinoline as nucleus of the alkaloids such as dictamine[2].



I

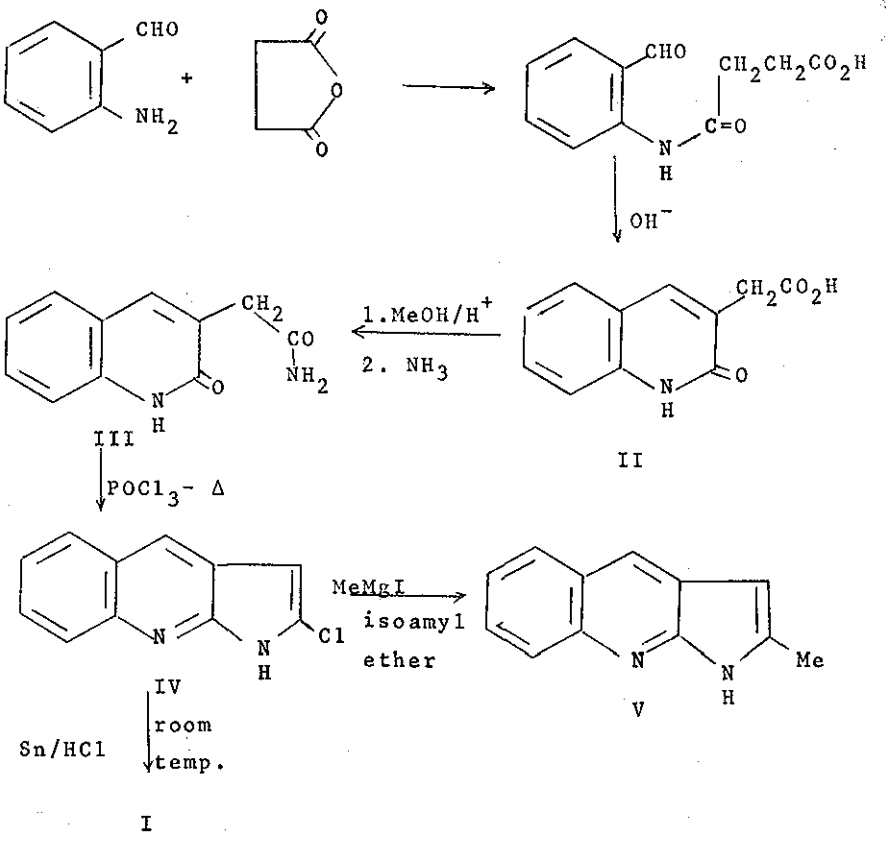
B. SYNTHESES

The first attempt at the synthesis of 1H-pyrrolo[2,3-b]quinoline was made by Perkin and Robinson. All their efforts to cyclize acetone quinol-2-ylhydrazone under the Fischer indole synthesis conditions were unsuccessful. In another attempt , starting from o-aminobenzaldehyde and succinic anhydride, they built up the carbostyril (II) which was in turn transformed to the amide (III) followed by its cyclization with phosphorous oxychloride to the chloroisoharman (IV) which when reduced led to I. Another reaction of IV gave isoharman (V). The scheme of Perkin and Robinson[1] is presented in chart 1.

A recent investigation[3] has, however, shown that the compounds obtained by Perkin and Robinson were uncyclized quinolines (see later).

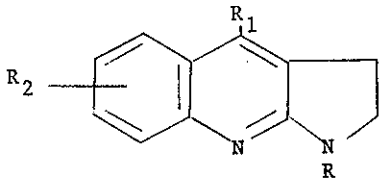
B.1 Reduced 1H-pyrrolo[2,3-b]quinolines

chart 1



Various 2,3-dihydro-1H-pyrrolo[2,3-b]quinolines have been obtained from carbostyrils and from 2,3-dihydrofuro[3,2-c]quinolines. Heating 3-(dialkylaminoalkyl)carbostyrils with appropriate halogen compounds such as phosphorous pentachloride and phosphorous oxychloride or with benzoyl chloride led to the N-alkylated 2,3-dihydro-1H-pyrrolo[2,3-b]quinolines (VI R=Et; R_1=Me; R_2=H, 6-OCOPh, 6-OMe, 7-Cl, 7,8-benzo)[4]. A similar reaction of 3-(acet-

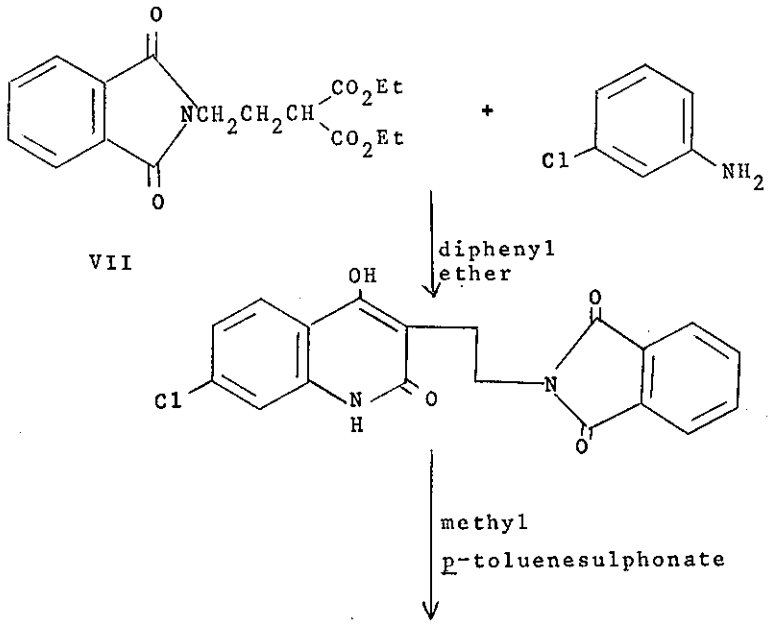
ylaminoethyl)carbostyril with phosphorous oxychloride led to VI (R=Ac or H; R_1=alkoxy; R_2=7-Cl)[5].

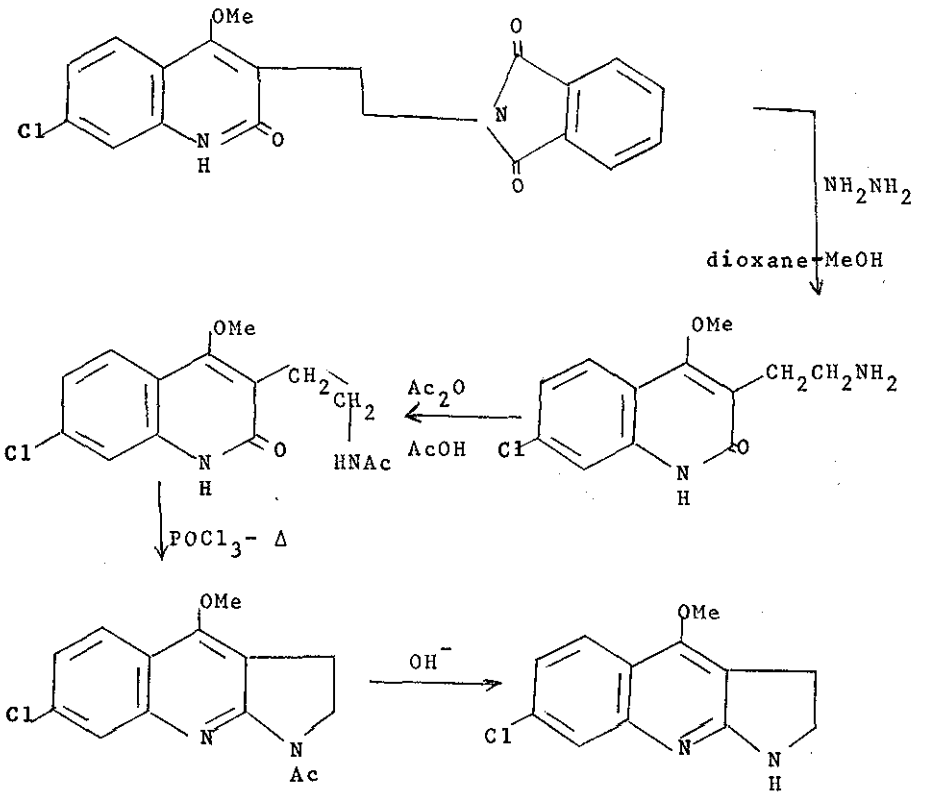


VI

In another related synthesis Tanaka and his co-workers starting from m-chloroaniline and diethyl 2-phthalylimidoethylmalonate (VII) prepared 2,3-dihydro-1H-pyrrolo[2,3-b]quinoline (VI, R=H, Ac; R_1= OMe; R_2=7-Cl) (chart 2)[6] and other derivatives of VI[7].

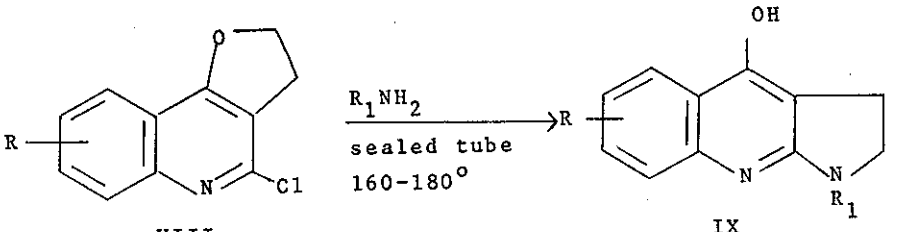
chart 2





When 2,3-dihydrofuro[3,2-c]quinolines (VIII) were treated with ammonia or with various amines, 2,3-dihydro-4-hydroxy-1H-pyrrolo-[2,3-b]quinolines were formed in good yields. These 1H-pyrrolo-[2,3-b]quinolines (IX) were methylated with diazomethane to give the corresponding X (chart 3)[8,9]. While treatment of trichloro-quinolines (XI) with amines resulted in the formation of other derivatives of 2,3-dihydro-1H-pyrrolo[2,3-b]quinolines (XII, chart 4)[8-10]. Carrying out these reactions under milder conditions a mixture of cyclized and uncyclized products was obtained[8].

chart 3

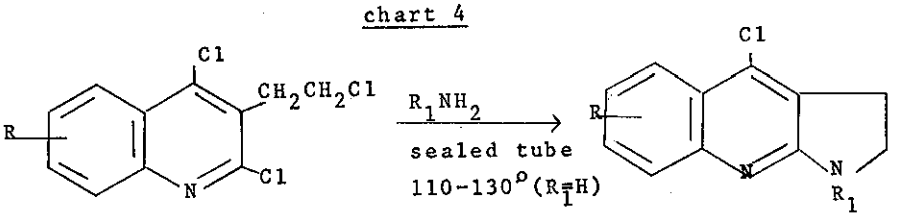


X

R=H, 6-Cl, 7-Cl,
6-OMe, 7-OMe

R_1=H, Me, CH_2Ph

chart 4



XII R=H, 6-Cl, 7-Cl, 6-OMe,
7-OMe, 8-OMe

R_1=H, CH_2Ph

The synthesis of 2,3,3a,4-tetrahydro-1H-pyrrolo[2,3-b]quinoline was accomplished by Loev et al.[11] as shown in chart 5.

The 2,3,3a,4,9,9a-hexahydro-1H-pyrrolo[2,3-b]quinoline (XV, R and R_1= lower alkyls) was formed in a reaction of a substituted carbostyril (XIV) with sodium in alcohol (chart 6)[12].

chart 5

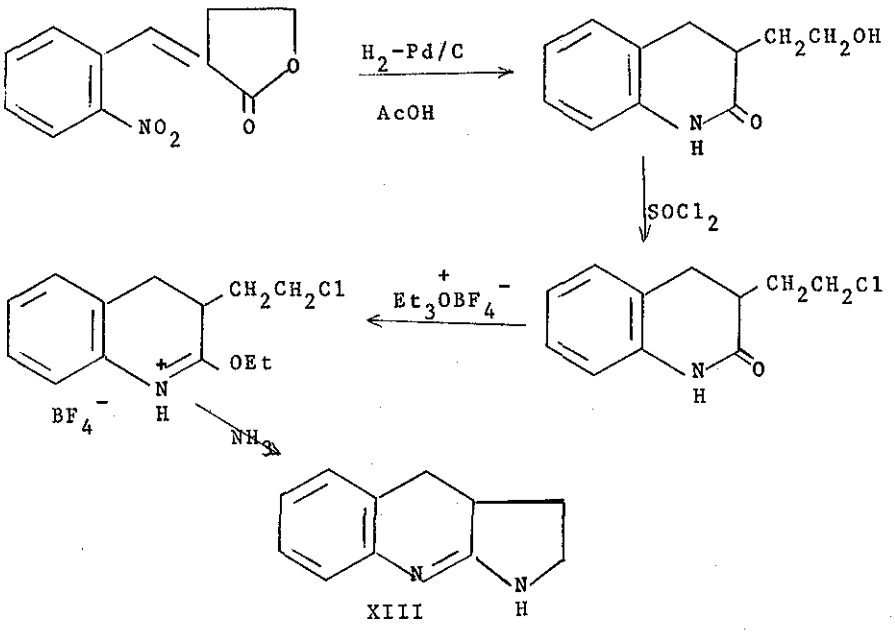
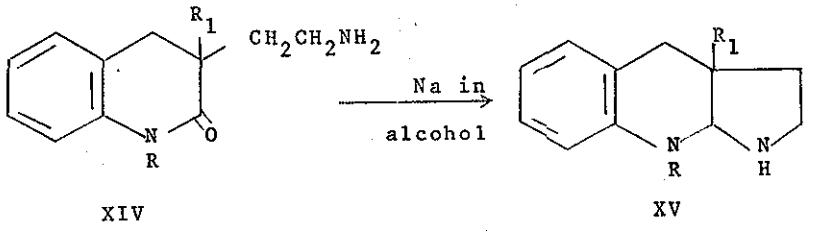


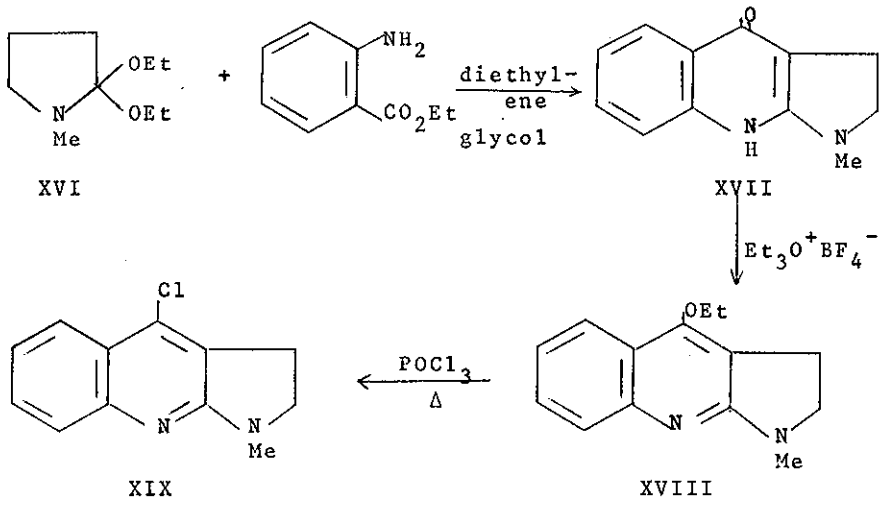
chart 6



In an attempted condensation of o-aminobenzophenone and ω-hydroxyalkanoic acids with polyphosphoric acid, the normal Friedländer products - 4-phenylquinolines were obtained together with some N-aryl-2,3-dihydro-1H-pyrrolo[2,3-b]quinolines[13].

In a reaction of N-methylpyrrolidin-2-one diethyl acetal (XVI) with ethyl anthranilate in diethylene glycol at 180-200°, 2,3,4,9-tetrahydro-4-oxo-1H-pyrrolo[2,3-b]quinoline (XVII) was obtained in 43% yield. XVII on treatment with triethyloxonium fluoroborate gave the corresponding 4-ethoxy derivative (XVIII) which was later transformed into 4-chloro derivative (XIX) by refluxing with phosphorous oxychloride (chart 7)[14].

chart 7

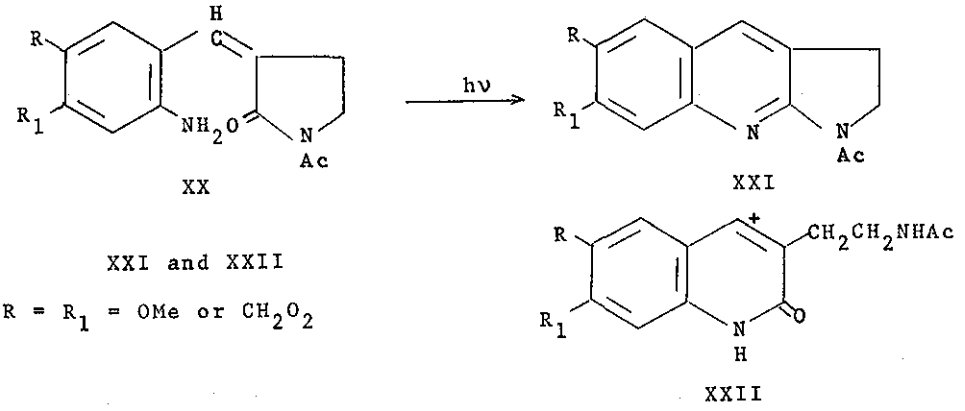


Finally irradiation of pyrrolidone (XX) gave good yield of 2,3-dihydro-1H-pyrrolo[2,3-b]quinoline (XXI) together with the corresponding carbostyril (XXII) (chart 8)[15].

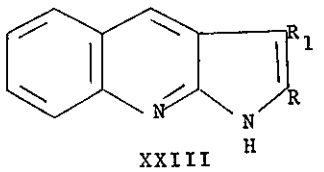
B.2 Totally aromatic 1H-pyrrolo[2,3-b]quinolines

Although Perkin and Robinson[1] as well as Fargher and Furness[16] had reported failure of the Fischer's indolization method as

chart 8



applied to quinol-2-ylhydrazones under variety of conditions, Grandberg and Yaryshev in 1969 had claimed the synthesis of 2-methyl-3-(β-aminoethyl)-1H-pyrrolo[2,3-b]quinoline (XXIII, R=Me, R_1=$CH_2CH_2NH_2$) from quinol-2-ylhydrazine and methyl γ-chloropropyl ketone[17]. However, recently Parrick and Wilcox[18] attempted to



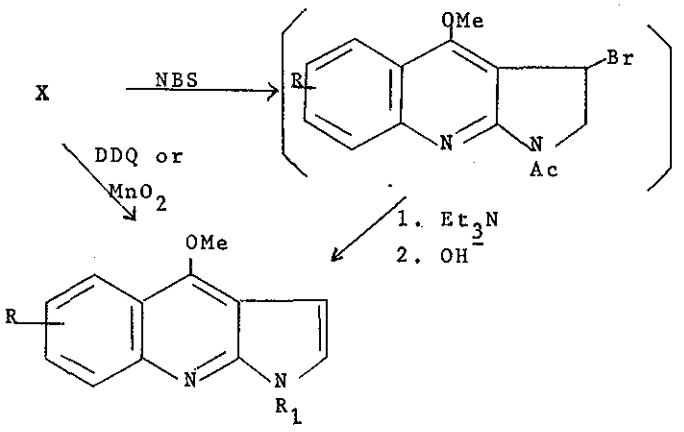
XXIII

prepare XXIII (R=R_1=Me and R=R_1=Ph) from quinol-2-ylhydrazones by a similar method but were unsuccessful in their attempts and instead 2-aminoquinoline and 2,3-diphenylimidazo[1,2-a]quinoline

among hosts of other products were isolated from their reactions.

Tanaka and co-workers were able to synthesize the completely aromatic 1H-pyrrolo[2,3-b]quinoline (I) either by dehydrohalogenation[3], or by oxidation with 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (DDQ)[3] or with manganese dioxide[3,19] (chart 9). Thus X (R=H or 7-Cl; R_1=Ac) was brominated with N-bromosuccinimide (NBS) to give an unstable bromo compound which on treatment with triethylamine followed by hydrolysis gave XXIV (R=H, 7-Cl; R_1=H), while X (R=7-Cl; R_1=CH_2Ph) on oxidation with DDQ or with manganese dioxide gave XXIV (R=7-Cl; R_1=CH_2Ph). A similar oxidation of XII (R =7-Cl ; R_1 =H) with manganese dioxide gave 4-chloro-1H-pyrrolo[2,3-b]quinoline.

chart 9

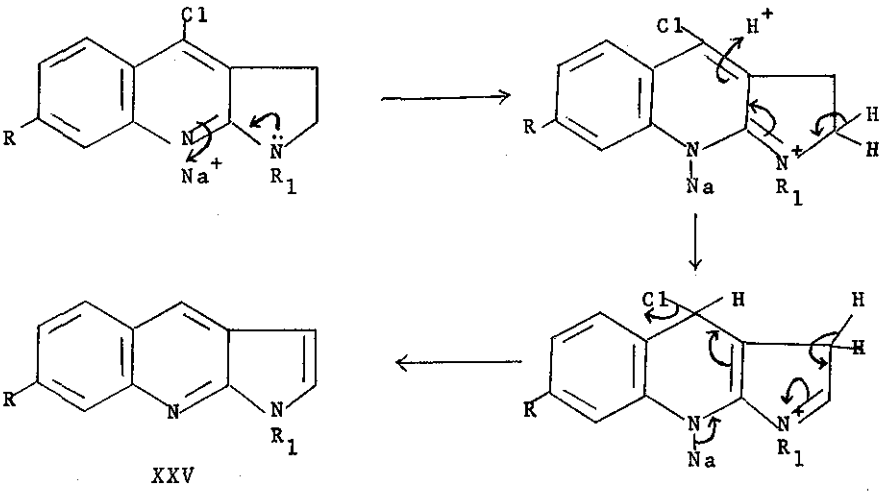


XXIV

When XII (R=H, 7-Cl; R_1=H) was treated with sodium methoxide in diglyme at 110-120°, X (R=H, 7-Cl; R_1=H) was formed together with unexpected dehydrohalogenation products - the totally aromatic 1H-pyrrolo[2,3-b]quinolines (XXV). This unexpected dehydro-

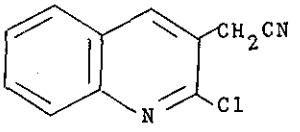
halogenation also ocurred in aprotic solvents such as N,N-dimethylformamide and dimethyl sulphoxide. The mechanism as advanced by Tanaka et al.[3] is presented in chart 10.

chart 10

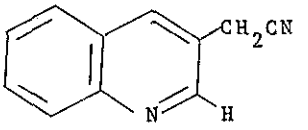


XXV

The completely aromatic parent ring system (XXV, $R=R_1=H$) thus obtained by Tanaka et al.[3] was not identical with the one reported by Perkin and Robinson[1] and to compare the two products the reaction scheme due to Perkin and Robinson was repeated only to find out that the compounds IV and I of chart 1, obtained by earlier workers were not the 1H-pyrrolo[2,3-b]quinolines but were indeed the uncyclized nitriles XXVI and XXVII respectively as both these compounds showed absorption bands at 2280 cm^{-1} due to the presence of cyano groups.



XXVI



XXVII

C. REACTIONS

Since the totally aromatic system has only recently been reported not many reactions have been performed on it. It seems reasonable to assume that the pyrrole ring of the system would be more prone to the electrophilic attack as compared to the rest of the molecule. The majority of the reported reactions however are the reactions of the substituents or of the dihydro-1H-pyrrolo[2,3-b]-quinoline such as oxidation of the dihydro system[3,19] already mentioned above, demethylation of the 8-methoxy derivative[20], substitution of the 4-chloro group by hydroxy[3], alkoxy[3,21] or amino groups[22,23], and N-alkylation[24].

A Birch reduction of XII (R=H; R_1=H) gave the tetrahydro derivative (XIII) while that of XII (R=H; R_1=CH_2Ph) resulted in the formation of VI (R=R_1=R_2=H)[3].

7-Chloro-4-methoxy-2,3-dihydro-1H-pyrrolo[2,3-b]quinoline has been condensed with ethyl acrylate and later converted into 3a,10b-diazacyclopenta[j,k]phenanthrene derivative[6].

D. SPECTRA

D.1 Ultraviolet Spectra

The ultraviolet spectra of the 2,3-dihydro compounds IX (R=H;

R_1=Me) and X (R=H; R_1=H and R=H; R_1=Me) were measured in methanol to establish the predominant "oxo" or "hydroxy" form of these compounds. It was revealed that the compound IX (R=H; R_1=Me) exists mainly in the 4-oxo form rather than in the 4-hydroxy form[8]. The ultraviolet spectra of the compounds XVII-XIX (chart 7) had also been measured in ethanol[14]: λ_{max} nm (log ε), XVII, 223 (4.5); 243 (4.5); 320 (4.2). XVIII, 255 (4.6); 276 (4.0); 338 (3.8), and XIX, 256 (4.5); 278 (4.0); 350 (3.9); 366 (3.8).

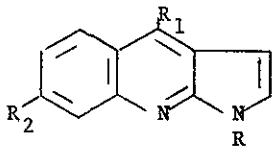
The reported ultraviolet spectra of the totally aromatic system are presented in Table 1 together with the other spectral data.

D.2 Proton Magnetic Resonance Spectra

The proton magnetic resonance spectra of various 2,3-dihydro compounds had been reported[8]. These were measured to help establish the structure of IX (R=Cl; R_1=H) and its 9-N-methyl derivative where C_5 proton (δ 8.32, d, J=9 Hz) was shown to have a downfield shift of 0.54 ppm when compared with that of 1-acetyl derivative of O-methyl analog X (R=Cl; R_1=Ac) (δ 7.78, d, J=9 Hz) because of the anisotropic deshielding due to the 4-oxo group in the former compound. Also these spectral data together with those of the other compounds established that the compounds obtained in the reaction of 2,3-dihydrofuro[3,2-c]quinoline were in fact the linear compounds rather than the angular ones.

The proton magnetic resonance spectrum of XIII has also been reported: δ 3.37, m, 2H, C_2H (DMSO-d_6) and δ 4.00, 2t, 2H, C_2H (TFA-d)[11]. The spectrum of XVIII has also been recorded in CCl_4[14]: δ 3.37, m, 2H, C_2H; 3.00, C_3H; 2.95, N-Me; 6.92-7.82, aromatic; 1.40 and 4.17, O-Et. The spectra of the totally aromatic system are

TABLE 1. SPECTRAL DATA OF 1H-PYRROLO[2,3-b]QUINOLINES



R	R_1	R_2	pmr δ	uv, $\lambda_{max.}$ nm(log ε) (in MeOH)	ir. cm^{-1} in nujol	Ref.
H	OMe	H	4.55(3H,s,OMe),6.82(1H,d,J=4Hz,C_3H); 7.23(1H,d,J=4Hz,C_2H); 8.18-7.29(4H,arom.). solvent: TFA-d/$CDCl_3$	246(4.94), 346(3.88).	1630,1610, 1580.	3
H	OMe	Cl	3.28(3H,s,OMe);6.85(1H,d,J=4Hz,C_3H); 7.16(1H,q,J=9 and 2Hz,C_6H);7.48(1H,d,J=4Hz, C_2H);7.73(1H,d,J=2Hz,C_8H);8.10(1H,d,J=9Hz, C_5H). solvent: DMSO-d_6	-	-	3
CH_2Ph	OMe	Cl	3.42(3H,s,OMe);5.45(2H,s,benzyl CH_2); 6.73 (1H,d,J=4Hz,C_3H);7.09(1H,d,J=4Hz,C_2H); 8.15-7.15(8H,arom.). solvent: $CDCl_3$	-	-	3
H	Cl	H	-	265(4.94), 316 sh.(3.88) 332(4.09)	-	3
H	H	H	6.70(1H,d,J=4Hz,C_3H);7.30-8.25(5H,arom.); 8.50(1H,s,C_5H). solvent: $CDCl_3$	-	-	3

TABLE 1 (contd.)

H	H	Cl	6.60(1H,q,J=4 and 1.5Hz,C_3H);7.34(1H,q,J=9 and 2Hz,C_6H);7.82(1H,q,J=4 and 1.5Hz,C_2H); 7.95(1H,d,J=2Hz,C_8H);8.00(1H,d,J=9Hz,C_5H); 8.48(1H,s,C_4H). solvent: DMSO-d_6	-	-	3
Me	[a]	H	1.80(2H,m,-$CH_2\underline{CH_2}CH_2$-);2.24(6H,s,NMe_2); 2.45(2H,t,$C\underline{H_2}N$);3.74(3H,s,NMe);3.86(3H,t, $HNCH_2$);6.59(1H,d,C_2H);6.87(1H,d,C_3H); 7.00-8.00(4H,m,arom.). solvent: $CDCl_3$	-	-	23

a) R_1 is $HNCH_2CH_2CH_2NMe_2$.

presented in the Table 1.

D.3 Infrared Spectra

The infrared spectra of the various dihydro compounds as reported by Tanaka et al.[8] are as follows: IX (R=7-Cl, R_1=H, N_9-Me), 1610, and 1580 cm^{-1}(nujol); IX (R=7-Cl, R_1=Ac, N_9-Me), 1655, 1615, and 1575 cm^{-1}(nujol); X (R=7-Cl, R_1=Ac), 1650, 1620, and 1570 cm^{-1} (nujol); XII (R=7-Cl, R_1=CH_2Ph), 1635, 1608 and 1564 cm^{-1}(nujol); XII (R=7-OMe, R_1=H), 1640, 1610, and 1590 cm^{-1}(nujol). Zhidkova and co-workers[14] have reported the infrared spectra of three 2,3-dihydro-1H-pyrrolo[2,3-b]quinolines in vaseline (nujol?) as follows: XVII, 1580 (C=C), 1635 (C=O amide), 2700-2500 cm^{-1}(NH associated); XVIII, 1635 (C=N); and XIX, 1650 cm^{-1}(C=N).

The infrared of one fully aromatic system,as reported, is included in the Table 1.

E.BIOLOGICAL ACTIVITY

During the biological testing of the many reduced 1H-pyrrolo-[2,3-b]quinolines it was revealed that these contain some of the following properties: antiinflammatory and analgesic[5,7,9,22], analgesic[10], antiinflammatory[20,21], antibacterial[20], antihypertensive[11], antipyretic[7], anticonvulsant[12], and interferon inducing activity[23]. None of the compounds tested, however, seem to have been tested clinically.

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