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

Misbahul Ain Khan* and João Ferreira da Rocha

Seção de Química, Instituto Militar de Engenharia,

Urca, Rio de Janeiro, RJ, Brasil

This article presents a survey of the chemistry of 1H-pyrrolo[3,2-b]quinoline system. Various routes for the synthesis of the totally aromatic as well as the reduced 1H-pyrrolo[3,2-b]quinolines are also included. Spectral data for the known compounds are reported.

CONTENTS

D.3 Infrared spectra

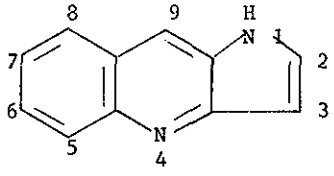
D.4 Mass spectra

E. X-RAY

F. BIOLOGICAL ACTIVITY

A. INTRODUCTION

Since no natural product seems to contain 1H-pyrrolo[3,2-b]quinoline skeleton (I), relatively little work has been done on this system. The earlier work of synthesis was done to find new antimalarial drugs analogous to quinine and harmaline[2]. Later on the synthesis of 1-methyl-1H-pyrrolo[3,2-b]quinoline was carried out to establish the identity of a base with molecular formula $C_{12}H_{10}N_2$ obtained during the degradation of calycanthine but was found to be non identical and hence eliminating the possibility of 1H-pyrrolo[3,2-b]quinoline as being the basic skeleton of calycanthine[3].



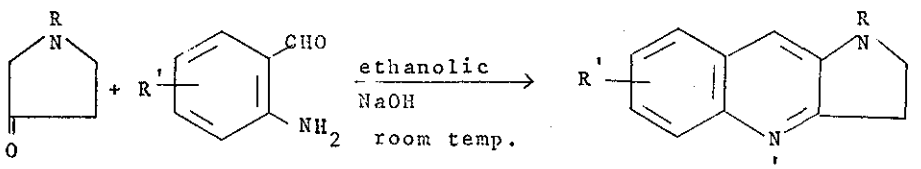
I

B. SYNTHESES

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

The only reduced 1H-pyrrolo[3,2-b]quinolines reported in the literature were obtained by a Friedländer base-catalyzed condensation of o-aminobenzaldehyde with pyrrolidin-3-ones (II) (chart 1). The yield of III varied : 5% (from IIa) to nearly quantitative

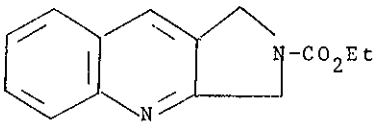
chart 1



IIa R=Ac
IIb R=CO_2Et

IIIa R=Ac, R'=H
IIIb R=CO_2Et, R'=H
IIIc R=R'=H
IIId R=CO_2Et, R'=6-OMe
IIIe R=CO_2Et, R'=7-OMe

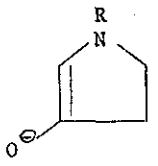
(from IIb). In the case of IIb the ratio of IIIc to IIIb depended upon the conditions of the reaction. Using 1% ethanolic sodium hydroxide IIIb was formed in 20% yield while with a 12% ethanolic sodium hydroxide solution it was not isolated from the reaction. The isomeric 2H-pyrrolo[3,4-b]quinoline (IV) was however formed in these reactions in respective yields of 15 and 19% together with IIIb and IIIc. When acid catalysts were used in the above synthesis, the predominant formation of IV was observed in these reactions. The 6- and 7-methoxy derivatives (IIId and IIIe) were also synthesized, albeit in low yields, by similar reactions. The compound IIIc is formed by hydrolysis of IIIb during the course of the reaction[4]. The predominant formation of IIIa and IIIb under



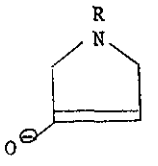
IV

basic reaction conditions was explained as due to the greater

stability of the enolate ion Va as compared to Vb[5]. Also under the acid catalysed condensations IIIc was not formed since the conditions were not favorable for hydrolysis[4].



Va

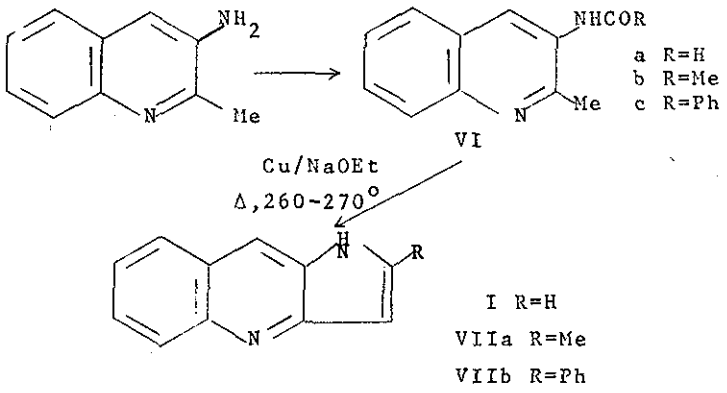


Vb

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

The first synthesis of totally aromatic system I was accomplished by Robinson et al. who obtained 3-acylamino-2-quinaldines (VI) from a reaction of 3-amino-2-quinaldine with formic acid, acetic anhydride, or benzoyl chloride. When VIa-VIc were treated with sodium ethoxide at a temperature of 260-270° in the presence of copper powder, I, VIIa , and VIIb were formed in the yields of

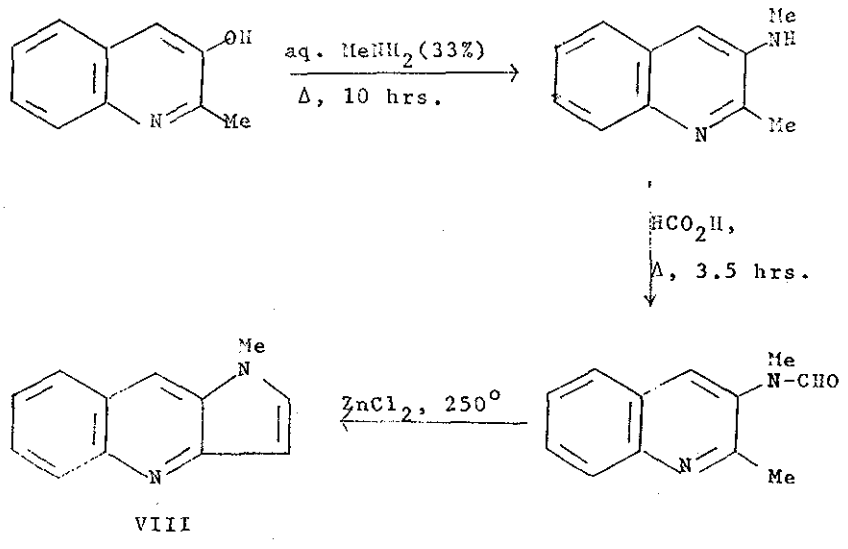
chart 2



22, 22, and 42% respectively. Cyclizing agents such as zinc chloride or sodium in hot xylene as well as phosphoryl chloride, phosphorous pentoxide, fused potassium acetate, or sodium amide failed to bring about the cyclization of VI[2] (chart 2).

Although Robinson et al.[2] had been unable to cyclize their 3-acylamino-2-quinaldines (VIa-VIc) by using zinc chloride as the cyclizing agent, Eiter and Nagy[3], however, were successful in their attempts to obtain VIII under these conditions. Their synthetic scheme is presented in chart 3. The compound VIII was isolated in 7.5% overall yield (starting from 3-hydroxy-2-quinaldine).

chart 3

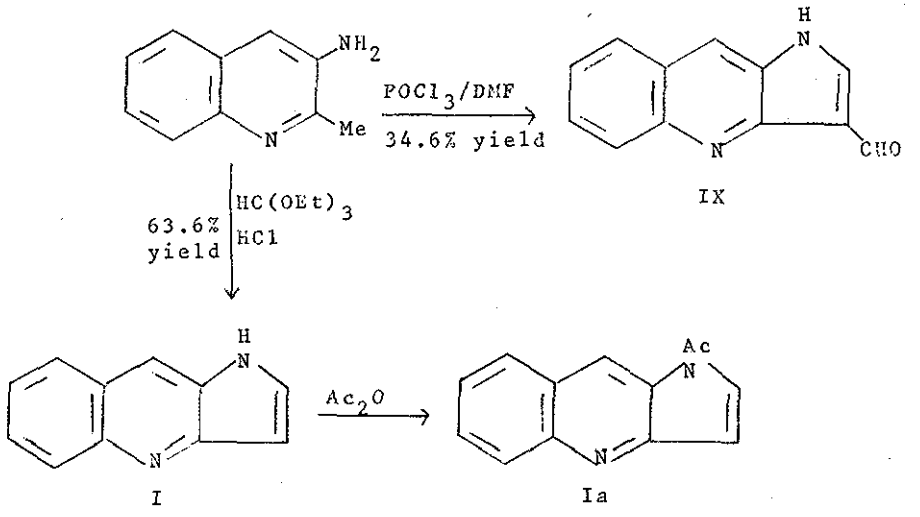


VIII

In two other routes to the aromatic system, and still using 3-amino-2-quinaldine, Parrick and co-workers obtained, in one step, the 3-formyl-1H-pyrrolo[3,2-b]quinoline (IX) by a reaction of phosphoryl chloride and N,N-dimethylformamide[6]. The basic ring

system (I), reported earlier by Robinson et al.[2], was also obtained by Parrick and co-workers in a reaction of triethyl orthoformate with the aminoquinaldine[7]. The products IX and I were obtained in good yields (chart 4).

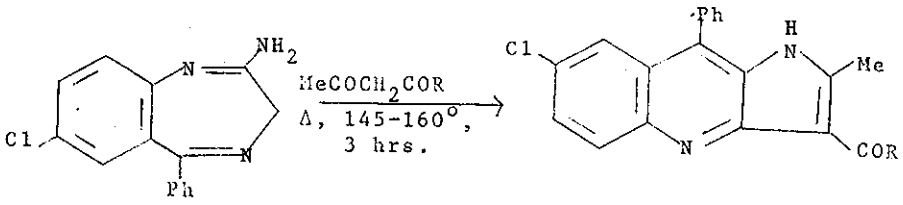
chart 4



Finally, 3-acyl-1H-pyrrolo[3,2-b]quinolines (XIa-XIc) were recently obtained in a reaction of 2-amino-7-chloro-5-phenyl-3H-1,4-benzodiazepine (X) with 1,3-dicarbonyl compounds in yields of 24.2, 11.5, and 32% respectively (chart 5). These products are the result of a rearrangement. To explain the formation of XIa-XIc Szmuszkovicz et al. proposed a mechanism for this rearrangement which is presented in the chart 6[8].

These workers tried to synthesize 7-chloro-2-methyl-9-phenyl-1H-pyrrolo[3,2-b]quinoline (XIII) from XII (chart 7) but only trace of XIII together with its monochloro derivative was detected in the mass spectrum of the mixture obtained on refluxing XII with

chart 5



X

XIa R=OEt
XIb R=Ot-Bu
XIc R=Me

chart 6

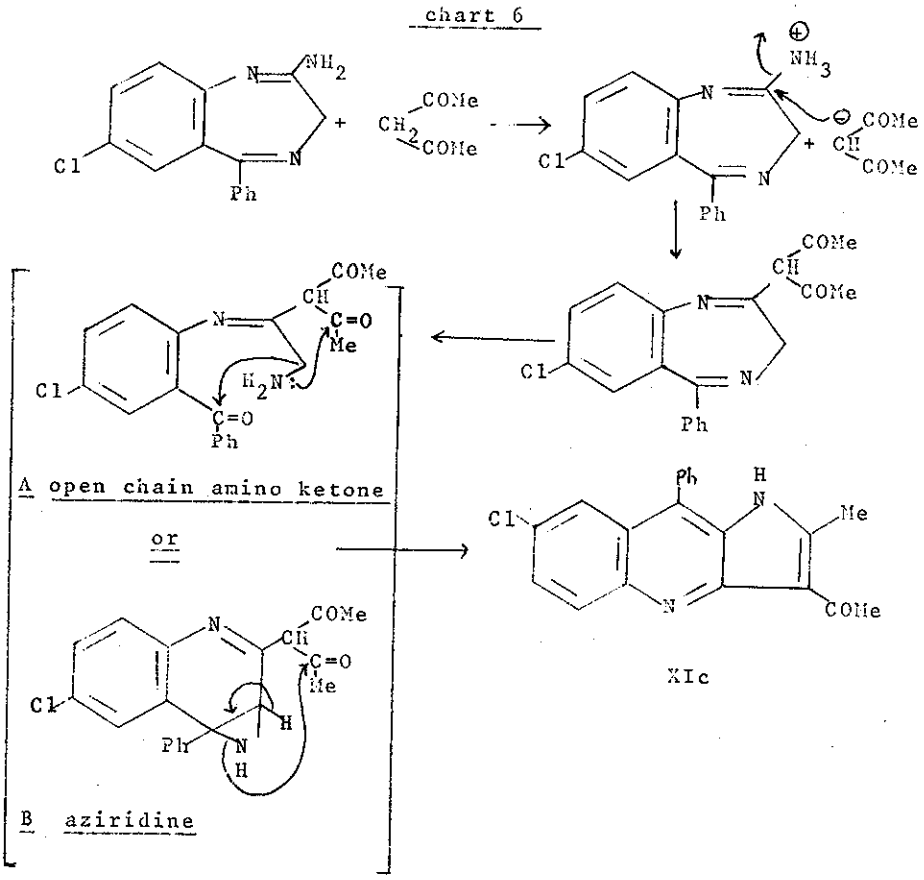
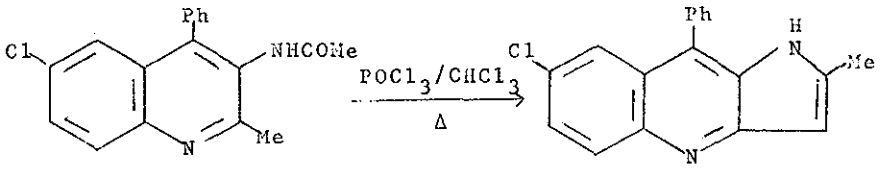


chart 7



XII XIII

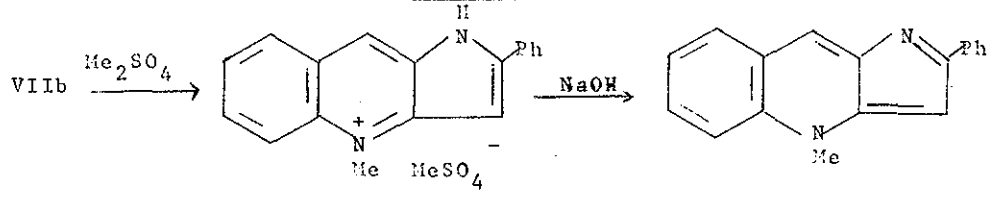
phosphoryl chloride followed by treatment with trimethylamine. The reaction of XII with potassium t-butoxide at 255-270° also gave only a trace of XIII as was detected in the mass spectrum of the reaction mixture[8].

C. REACTIONS

C.1 N-Alkylation

Robinson and co-workers[2] found that VIIb on treatment with dimethyl sulfate gives a quaternary salt XIV which when treated with sodium hydroxide gives the "anhydronium base"- 4-methyl-4H-pyrrolo[3,2-b]quinoline (XV) (chart 8). The alkylation of XIa has also

chart 8

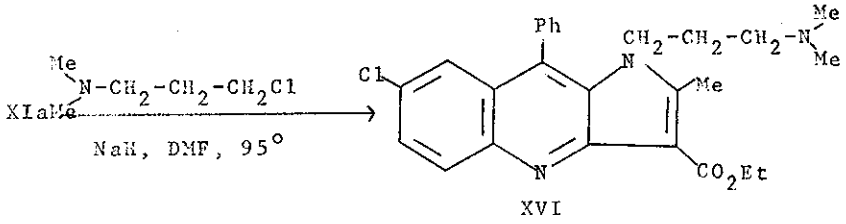


XIV XV

been carried out in N,N-dimethylformamide using 3-N,N-dimethylaminopropyl chloride in the presence of sodium hydride to give ethyl 7-chloro-1-(3-N,N-dimethylaminopropyl)-2-methyl-9-phenyl-1H-pyrro-

lo[3,2-b]quinoline-3-carboxylate (XVI) in 22% yield[8] (chart 9).

chart 9

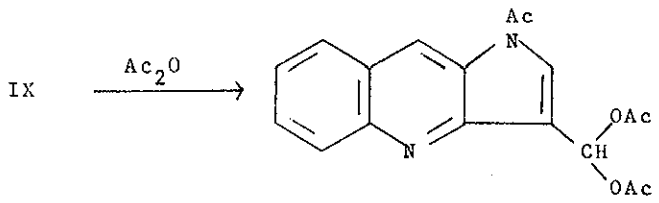


XVI

C.2 N-Acylations

The compound IIIc when treated with acetic anhydride gave the corresponding N-acetyl compound IIIa[4]. On acetylation the compound IX gave the N-acetyl derivative XVII in 40% yield[6] (chart 10). The

chart 10



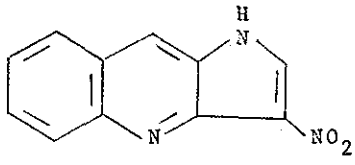
XVII

acetylation of I, however, resulted in the expected N-acetyl product Ia[7] (chart 4).

C.3 Electrophilic substitutions

The formylation of I under Vilsmeier-Haack conditions gave 61.2% yield of IX[7], which was identical with the cyclization product of the reaction of 3-amino-2-quinaldine with N,N-dimethyl-formamide in the presence of phosphoryl chloride described

earlier[6]. The nitration of I has also been carried out in fuming nitric acid at 0° to give 3-nitro-1H-pyrrolo[3,2-b]quinoline. The yield of XVIII was not recorded however[7].

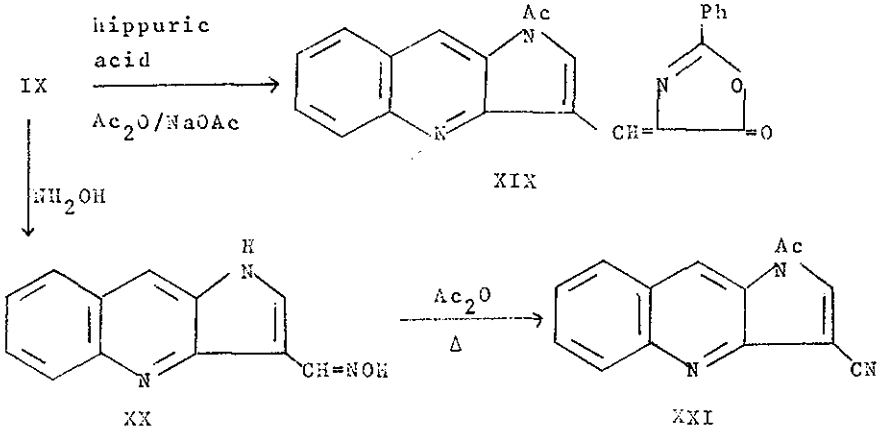


XVIII

C.4 Modification of substituent

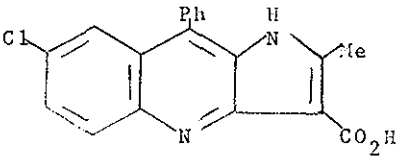
Relatively few modifications of the groups of the recorded 1H-pyrrolo[3,2-b]quinolines have been carried out. The aldehyde group of IX has been modified by reaction with hippuric acid in the presence of acetic anhydride to give the azalactone XIX. The conversion of the aldehyde to an oxime was also carried out. The oxime XX on heating in acetic anhydride under reflux gave the corresponding nitrile XXI[6] (chart 11).

chart 11



XIX XX XXI

The hydrolysis of the ester XIb was accomplished by treatment with trifluoroacetic acid and the corresponding acid (XXII) was obtained in 70% yield[8].



XXII

D. SPECTRA

D.1 Ultraviolet spectra

The recorded ultraviolet spectra for the various 1H-pyrrolo-[3,2-b]quinolines are presented in Table 1 together with their extinction coefficients (log ε) and the solvent used for the measurement of the spectra. The ultraviolet spectra of the compounds XIa, XIb, and XIc were very similar to each other and thus indicating that these compounds posses the same chromophore and belong to the same basic structure . This lent more support for the proposed structures for the rearrangement products[8].

D.2 Proton magnetic resonance spectra

The proton magnetic resonance spectra of the various derivatives of 1H-pyrrolo[3,2-b]quinolines (both the reduced as well as the totally aromatic compounds) have been reported in the literature and these are tabulated in the Table 2. The spectra were of special help in elucidating the structures of the rearranged products derived from a reaction of the diazepine X with various 1,3-dicarbonyl compounds[8].

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

compd. No.	$\lambda_{max.}$ nm (logε)	solvent	Ref.
IIId	270(4.08), 346(3.98), and 355(4.00).	MeOH	4
IIIe	250(4.81) and 329(4.18).	MeOH	4
IX	280(4.20), 329(4.06), and 355(3.88).	MeOH	6
XIa	238 sh.(4.61), 249(4.73), 334(4.10), 354(3.98), and 368 sh.(3.92).	EtOH	8
XIb	205(4.54), 238 sh.(4.59), 252(4.72), 320 sh. (3.87), 334(4.09), 354(3.97), and 367 sh.(3.91).	EtOH	8
XIc	209(4.44), 248(4.80),280(4.35), 319 sh.(3.87), 333(3.08), 355(4.00), and 369(3.95)	EtOH	8
XVI	230 sh.(4.45), 256(4.81), 322 sh.(3.81), 336 (4.08), 357(3.97), and 370 sh.(3.91).	EtOH	8
XXII	204(4.50), 236 sh.(4.60), 251(4.75), 332(4.11), 358(3.95), and 372 sh.(3.91).	EtOH	8

D.3 Infrared spectra

The infrared spectra of various 1H-pyrrolo[3,2-b]quinolines have been recorded in the literature. The NH absorption for the various derivatives was observed between 2900 and 3450 cm^{-1}, often as a broad band[8]. The other characteristic absorptions for the substituents had also been reported. The recorded data is accumulated in the Table 3.

TABLE 2. PROTON MAGNETIC RESONANCE SPECTRA OF 1H-PYRROLO[3,2-b]QUINOLINES
(δ, ppm)

compd. no.	NH	pyrrole ring protons	aromatic protons	other signals	solvent	ref.
I	11.50	6.70(2H,d,C_2H and C_3H)	7.50-8.00(4H,m); 8.30(1H,s,C_9H)	-	DMSO-d_6	7
Ia	-	6.70(1H,d,J=3Hz,C_3H); 6.90(1H,d,J=3Hz,C_2H)	7.20-8.20(4H,m); 8.40(1H,s,C_9H)	2.50(3H,s,COMe)	DMSO-d_6	7
IIIa	-	2.38(2H,t,J=8Hz,C_2H); 3.97(2H,t,J=8Hz,C_3H)	7.32-8.07(5H,m)	2.25(3H,s,COMe)	$CDCl_3$	4
IIIb	-	3.30(2H,t,J=9Hz,C_2H); 4.21(2H,t,J=9Hz,C_3H)	7.33-8.25(5H,m)	1.38(3H,t,J=7Hz, $CO_2CH_2C\underline{H}_3$); 4.37 (2H,q,J=7Hz, $CO_2C\underline{H}_2CH_3$)	$CDCl_3$	4
IIIc	4.18	3.00-3.85(4H,m,C_2H and C_3H)	6.73(1H,s); and 7.20-7.95(4H,m)	-	$CDCl_3$	4
IIId	-	-	7.50-8.10(4H,m)	1.38(2H?,t,J= 8Hz,$CO_2CH_2C\underline{H}_3$); 4.32(2H,q,J=7Hz, $CO_2C\underline{H}_2CH_3$)	$CDCl_3$	4
IIIe	-	3.00(2H,t,J=8Hz,C_2H); 3.75(2H,t,J=8Hz,C_3H)	7.10-8.00(4H,m)	1.25(3H,t,J=7Hz, $CO_2CH_2C\underline{H}_3$);4.20 (2H,q,J=7Hz, $CO_2C\underline{H}_2CH_3$);3.00 (OMe)	C_6D_6	4
IX	12.70	8.57(1H,s,C_2H)	7.46-8.29(4H,m); 8.91(1H,s,C_9H)	10.40(1H,s,$C\underline{H}O$)	DMSO-d_6	6

contd.

TABLE 2.(contd.)

XIa	10.71 (br.)	-	7.42-7.84(7H,m); 8.60(1H,d,J=9.5 Hz)	1.40(3H,t,J=7Hz, $CO_2CH_2\underline{CH}_3$);4.40 (2H,q,J=7Hz, $CO_2\underline{CH}_2CH_3$);2.80 3H,s,N-C-Me)	DMSO-d_6	8
XIb	-	-	-	1.80(9H,s,t-Bu); 2.83(3H,s,N-C-Me)	pyridine d_5	8
XIc	11.80 (br.)	-	7.43-7.80(7H,m); 8.07(1H,d,J=9.8 Hz)	2.74(3H,s,C-Me); 2.93(3H,s,COMe)	DMSO-d_6	8
XVI	-	-	7.60-7.71(7H,m); 8.24(1H,d,J=8.5 Hz)	1.25-1.76(4H,m, $CH_2\underline{CH}_2$-N-);1.52 (3H,t,$CO_2CH_2\underline{CH}_3$); 2.06(6H,s,$N\underline{Me}_2$); 2.86(3H,s,N-C-Me); 3.50-3.85(2H,m, pyrrole-N-$\underline{CH}_2$); 4.54(2H,q,J=7Hz, $CO_2\underline{CH}_2CH_3$)	$CDCl_3$	8
XVIII	11.50 (br.)	8.30(1H,s,C_2H)	7.60-8.40(4H,m); 9.00(1H,s,C_9H)	-	$CDCl_3$	7

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

compd. no.	infrared absorption cm^{-1}	ref.
I	3150(NH) (KBr)	7
Ia	1690(C=O) (KBr)	7
IIIa	1665(C=O);1610, and 1570 (KBr)	4
IIIb	1705(C=O);1615, and 1575 (KBr)	4
IIIc	3205(NH);1625, and 1575 (KBr)	4
IIId	1695(C=O) and 1625 (KBr)	4
IIIe	1700(C=O) and 1615 (KBr)	4
IX	3350(NH) and 1650(C=O) (KBr)	6
XIa	2900(br.,NH),1685(C=O);1630,1595,1550,1500(C=N/C=C); 1265,1170,1155,1140,1085,1040(C-O/C-N);830,780,740, and 700(arom.) (nujol)	8
XIb	2900(br.,NH);1685(C=O);1635,1600,1550,1505,1480(C=C/C=N);1270,1150,1140,1090,1020(C-O/C-N);830, and 795 (arom.) (nujol)	8
XIc	3320(NH);1640,1630(C=O/C=N);1600,1570,1540,1500(C=N/C=C);1300,1160,950(C-N);820,and 710(arom.) (nujol)	8
XVI	2810,2780,2760,2720(N-alkyl);1670(C=O);1610,1590, 1545,1485(C=C/C=N),1265,1225,1170,1120,1100(C-O/C-N); 830, and 710(arom.) (nujol)	8
XVII	1750(amideC=O), and 1710(acetateC=O) (KBr)	6
XVIII	3450(NH) (KBr)	7
XIX	1775 and 1701(C=O) (KBr)	6
XXI	2235(C≡N), and 1722(C=O) (KBr)	6

XXII 3140(br.),3050,2760,2700 sh.(NH/acid OH);1700(C=O);1625, 1600,1565(C=C/C=N),1290,1175,1165,1135,1075(C-O/C-N); 825,775, and 700(arom) (nujol) 8

D.4 Mass spectra

As regards the mass spectra the molecular ions of various 1H-pyrrolo[3,2-b]quinolines were reported in connection with the structural proof of the isolated products[4,6,8]. The mass spectra were used to support the structures of the rearranged products of the chart 5. The mass spectra gave a peak at m/e 41 (MeCN) which indicated the presence of a Me-C-N moiety and thus confirming the structures[8].

E. X-RAY

The structure of XVI was determined by single crystal x-ray analysis. It was found that the fused ring portion of the molecule is flat and the plane of the phenyl ring is approximately perpendicular (85 and 88°) to the plane of the fused rings while the carboxyl group is twisted about 10° out of the plane of the fused rings. The pattern of long and short bond lengths in the quinoline portion of the molecule is consistent with the values reported in the literature for quinoline and amidine ring systems and can be explained by resonance structures[8].

F. BIOLOGICAL ACTIVITY

No data is available on the biological activity of the reported 1H-pyrrolo[3,2-b]quinolines although the work of Robinson et al. was initiated in attempts to find new antimalarials[2].

REFERENCES

1. for part I, see M.A.Khan and J.F.da Rocha, Heterocycles,in print.
2. G.Barger, R.Robinson, and G.M.Robinson, J.Chem.Soc., 1929,2947.
3. K.Eiter and M.Nagy,Monatsch., 1949, 80, 607 (Chem.Abstr., 1951, 45, 627).
4. L.H.Zalkow, J.B.Nabors, K.French, and S.C.Bisarya, J.Chem.Soc. C, 1971, 3551.
5. E.A.Fehnel, J.Org.Chem., 1966, 31, 2899.
6. B.A.J.Clark, J.Parrick, P.J.West, and A.H.Kelly, J.Chem.Soc.C, 1970, 498.
7. J.Parrick and R.Wilcox, J.Chem.Soc.Perkin I, 1976, 2121.
8. J.Szmuszkovicz, L.Baczynskyj, C.C.Chidester, and D.J.Duchamp, J.Org.Chem., 1976, 41, 1743.

Received, 18th July, 1977