

PYRROLOQUINOLINES II¹. 1H-PYRROLO[3,2-b]QUINOLINES

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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.

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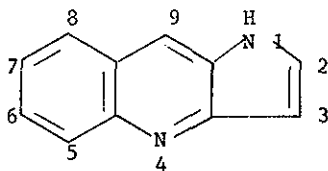
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A. INTRODUCTION

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 anti-malarial drugs analogous to quinine and harmaline². 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 calycanthine³.



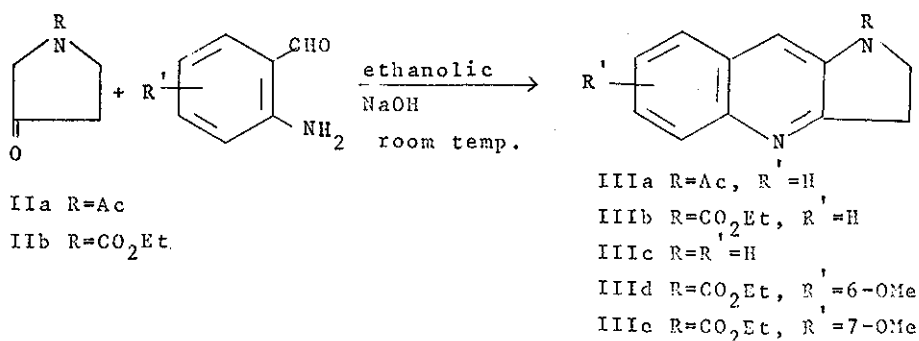
I

B. SYNTHESSES

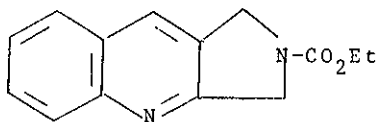
B.1 Reduced 1H-pyrrolo[3,2-b]quinolines

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



(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 reaction⁴. The predominant formation of IIIa and IIIb under



IV

basic reaction conditions was explained as due to the greater

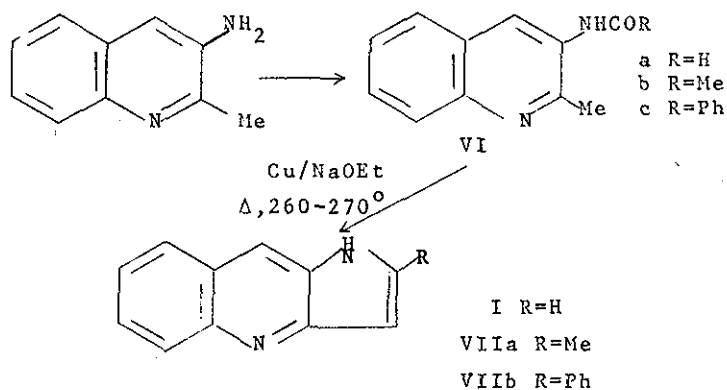
stability of the enolate ion Va as compared to Vb⁵. Also under the acid catalysed condensations IIIc was not formed since the conditions were not favorable for hydrolysis⁴.



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-quinolindines (VI) from a reaction of 3-amino-2-quinolindine 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

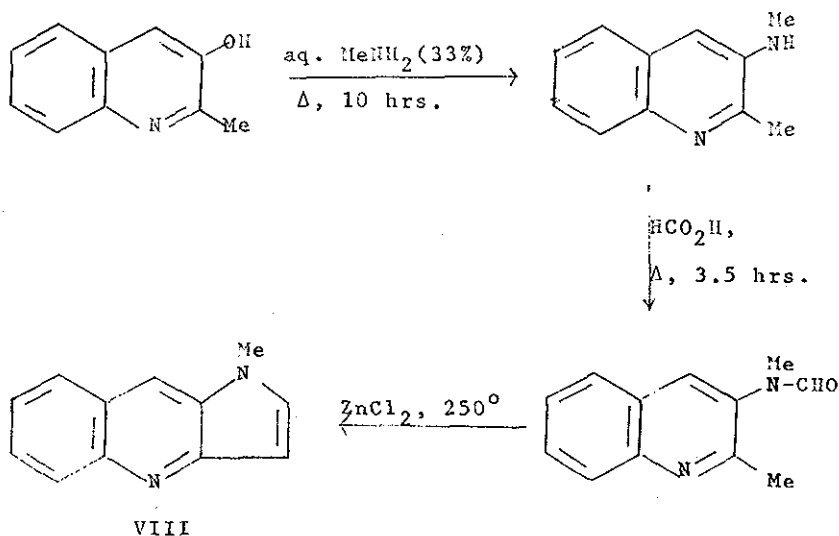
chart 2



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 VI² (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 Nagy³, 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).

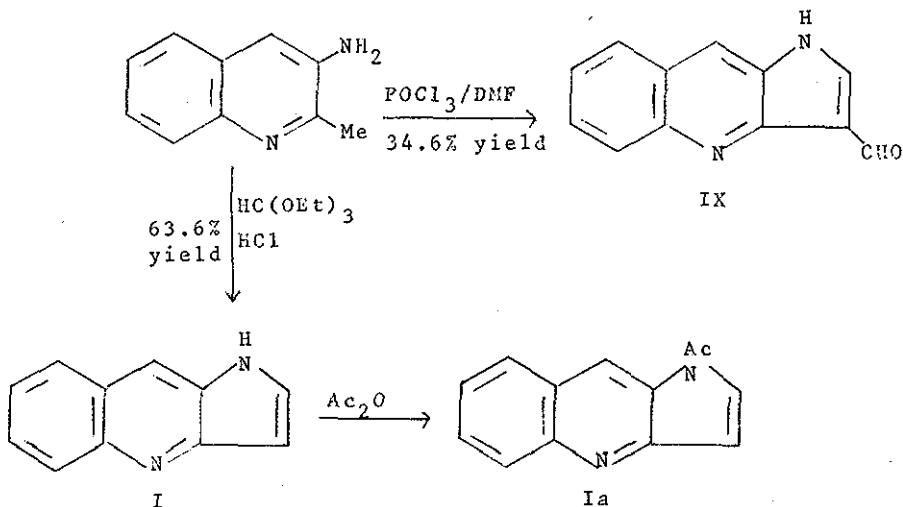
chart 3



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*-dimethylformamide⁶. 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 aminoquinoline⁷. The products IX and I were obtained in good yields (chart 4).

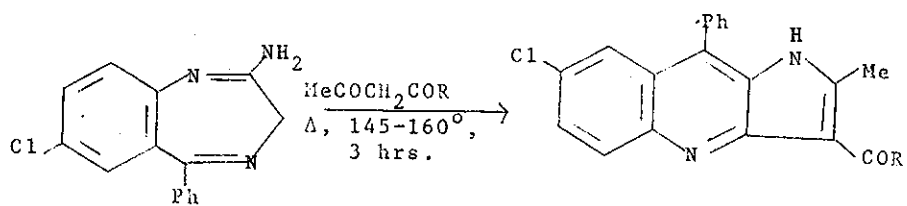
chart 4



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 6⁸.

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

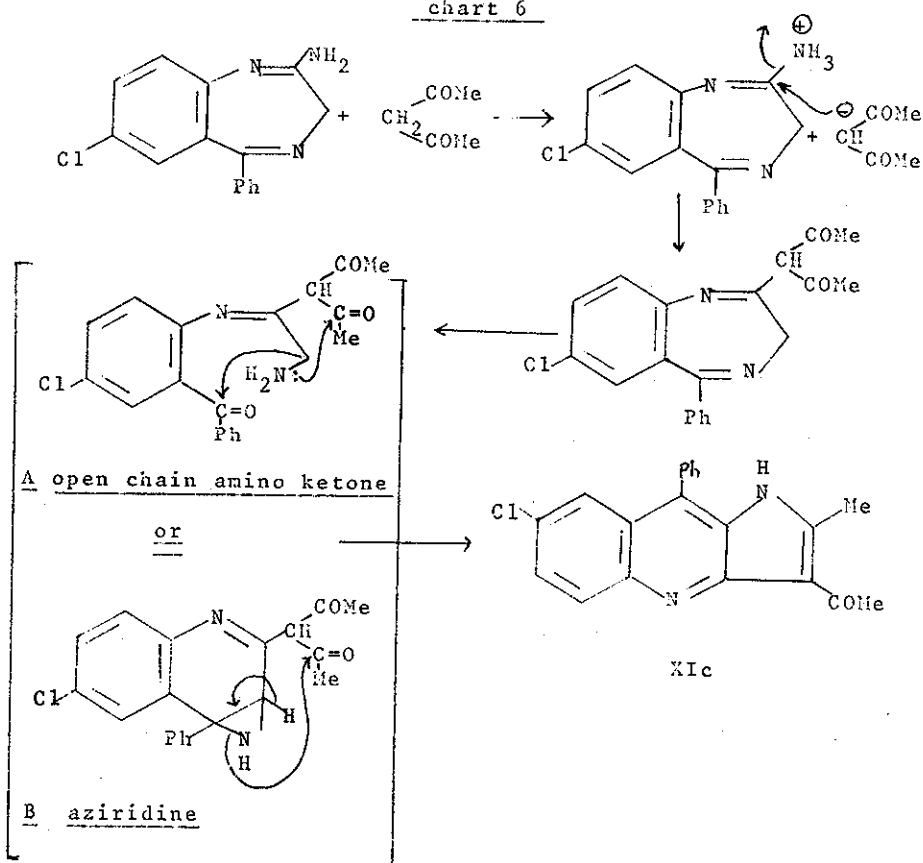
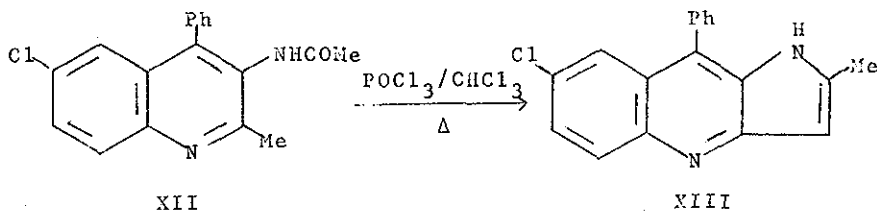


chart 7

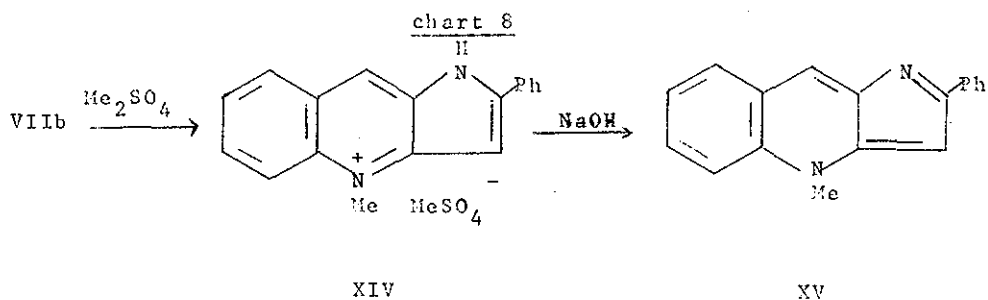


phosphoryl chloride followed by treatment with trimethylamine. The reaction of XII with potassium *t*-butoxide at 255-270° also gave only a trace of XIII as was detected in the mass spectrum of the reaction mixture⁸.

C. REACTIONS

C.1 N-Alkylation

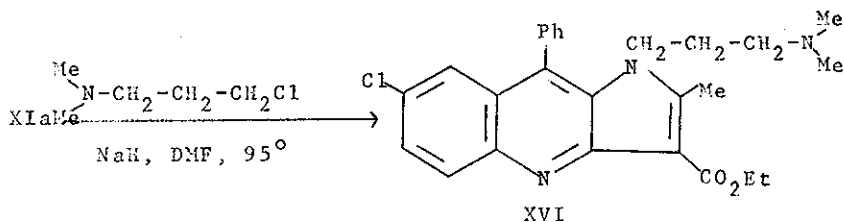
Robinson and co-workers² found that VIIb on treatment with dimethyl sulfate gives a quaternary salt XIV which when treated with sodium hydroxide gives the "anhydronium base"- 4-methyl-4H-pyrrolo[3,2-b]quinoline (XV) (chart 8). The alkylation of XIa has also



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-

to [3,2-b]quinoline-3-carboxylate (XVI) in 22% yield⁸ (chart 9).

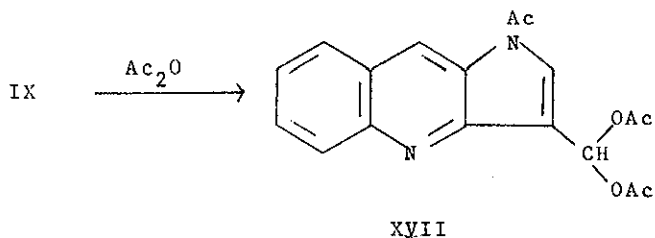
chart 9



C.2 N-Acylation

The compound IIIc when treated with acetic anhydride gave the corresponding N-acetyl compound IIIa⁴. On acetylation the compound IX gave the N-acetyl derivative XVII in 40% yield⁶ (chart 10). The

chart 10

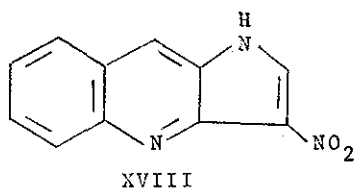


acetylation of I, however, resulted in the expected N-acetyl product Ia⁷ (chart 4).

C.3 Electrophilic substitutions

The formylation of I under Vilsmeier-Haack conditions gave 61.2% yield of IX⁷, which was identical with the cyclization product of the reaction of 3-amino-2-quininaldine with N,N-dimethylformamide in the presence of phosphoryl chloride described

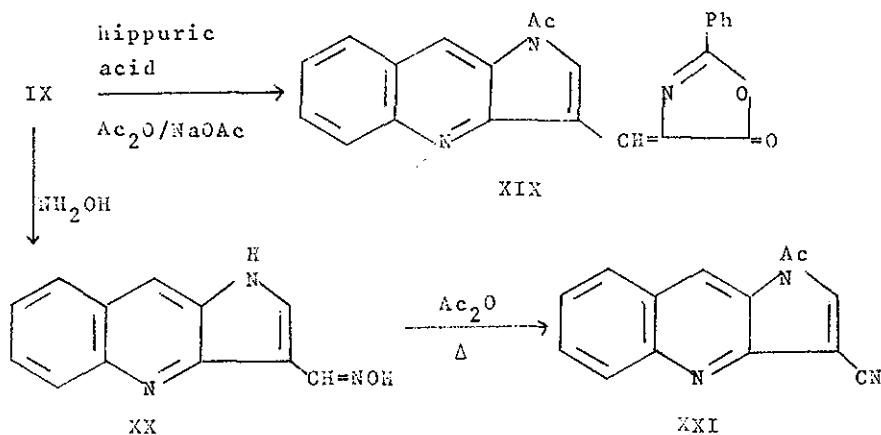
carrier⁶. The nitration of I has also been carried out in fuming nitric acid at 0° to give 3-nitro-1H-pyrrolo[3,2-b]quinoline. The yield of XVIII was not recorded however⁷.



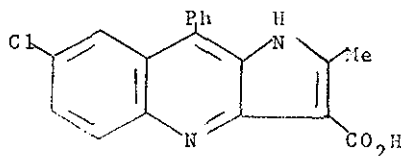
C.4 Modification of substituent

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 XXI⁶ (chart 11).

chart 11



The hydrolysis of the ester XIb was accomplished by treatment with trifluoroacetic acid and the corresponding acid (XXII) was obtained in 70% yield⁸.



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 possess the same chromophore and belong to the same basic structure. This lent more support for the proposed structures for the rearrangement products⁸.

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.	$\lambda_{\text{max.}}$ nm (log ϵ)	solvent	Ref.
IIIId	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 band⁸. 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 ₂ H and C ₃ H)	7.50-8.00(4H,m); 8.30(1H,s,C ₉ H)	-	DMSO-d ₆ 7
Ia	-	6.70(1H,d,J=3Hz,C ₃ H); 6.90(1H,d,J=3Hz,C ₂ H)	7.20-8.20(4H,m); 8.40(1H,s,C ₉ H)	2.50(3H,s,OMe)	DMSO-d ₆ 7
IIIa	-	2.38(2H,t,J=8Hz,C ₂ H); 3.97(2H,t,J=8Hz,C ₃ H)	7.32-8.07(5H,m)	2.25(3H,s,OMe)	CDCl ₃ 4
IIIb	-	3.30(2H,t,J=9Hz,C ₂ H); 4.21(2H,t,J=9Hz,C ₃ H)	7.33-8.25(5H,m)	1.38(3H,t,J=7Hz, CO ₂ CH ₂ CH ₃); 4.37 (2H,q,J=7Hz, CO ₂ CH ₂ CH ₃)	CDCl ₃ 4
IIIc	4.18	3.00-3.85(4H,m,C ₂ H and C ₃ H)	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 ₂ CH ₂ CH ₃); 4.32(2H,q,J=7Hz, CO ₂ CH ₂ CH ₃)	CDCl ₃ 4
IIIe	-	3.00(2H,t,J=8Hz,C ₂ H); 3.75(2H,t,J=8Hz,C ₃ H)	7.10-8.00(4H,m)	1.25(3H,t,J=7Hz, CO ₂ CH ₂ CH ₃); 4.20 (2H,q,J=7Hz, CO ₂ CH ₂ CH ₃); 3.00 (OMe) ₂	C ₆ D ₆ 4
IX	12.70	8.57(1H,s,C ₂ H)	7.46-8.29(4H,m); 8.91(1H,s,C ₉ H)	10.40(1H,s,CHO)	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, CH ₂ CH ₃); 4.40 (2H, q, J=7Hz, CO, CH ₂ CH 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 CH ₂ -N-); 1.52 (3H, t, CO, CH ₂ CH ₃); 2.06 (6H, s, NMe ₂); 2.86 (3H, s, N-C-Me); 3.50-3.85 (2H, m, pyrrole-N-CH ₂); 4.54 (2H, q, J=7Hz, CO, CH ₂ CH ₃)		8
XVIII	11.50 (br.)	8.30 (1H, s, C ₂ H)	7.60-8.40 (4H, m); 9.00 (1H, s, C ₉ H)	-	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 structures⁸.

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 structures⁸.

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 antimalarials².

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