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The reaction between quindoline-ll-carboxylic acid and alcohols in acid media gives the quindoline-ll-carboxylate esters, but quindoline-ll-carboxylic acid or its hydrochloride react with haloalkanes in the presence of basic catalysts and water binders to give 10-alkylquindoline-ll-carboxylate esters. 10-Alkyl-quindolines were obtained similarly. Alkylation of l-alkylquindoline-ll-carboxylate esters in neutral media affords the quaternary salts.

The possibility of using derivatives of quindoline-ll-carboxylic acid and quindoline in the manufacture of components of electrophotographic layers led us to examine synthetic routes to these compounds. Quindoline-ll-carboxylic acid (I) is one of the most readily accessible derivatives of quindoline [1-6]. There have been no reports of its alkylation, only its reaction with methyl iodide to give the quindoline quaternary salt having been described.

The acid (I) was obtained by reacting isatin with NO-diacetylindoxyl [6], but it was isolated from the reaction mixture as its potassium salt, which was then converted into the acid (I) or its hydrochloride.

In order to obtain hitherto unknown derivatives of indolo[3,2-b]quinoline, we examined the alkylation of the acid (I) and quindoline (II). Heating the acid (I) with ethanol or 1-butanol in the presence of concentrated sulfuric acid gave the quindoline-ll-carboxylate esters (IIIb, c). The reaction of (I) with 1-butanol was carried out in benzene with azeo-tropic removal of the water formed.

ROH H COOH III a-C

III a $R = CH_3$, b $R = C_2H_5$, c $R = p \cdot C_4H_9$; X = CI, Br

The methyl and ethyl esters of quindoline-ll-carboxylic acid (IIIa, b) were also obtained by reacting the acid (I) with alkyl halides in the presence of potassium hydroxide and calcium oxide in DMF at 20°C. The identity of the esters (IIIb) obtained by the two methods was established by TLC and the melting point of a mixed sample.



 $IVa R = p-C_4H_9$, b $R = CH_2(CH_2)_5CH_3$, c $R = CH_2C_6H_5$, d $R = CH_2CH = CH_2$; X = CI, Br

Treatment of the acid (I) with alkylating agents in ethyl methyl ketone in the presence of potassium hydroxide and calcium oxide at 65°C gave both the ester, and products alkylated at the nitrogen of the five-membered ring, to give the quindolines (IVa-d).

It was established by TLC that even after 20-30 min from the commencement of the reaction, new compounds were formed, and after 3-5 h the alkylation of the acid (I) under these conditions had proceeded to completion. This method enables 10-substituted quindolinecarboxylic acids to be obtained. The resulting esters (IVa-d) are soluble in benzene, toluene, acetone, ether, chloroform, methylene chloride, dichloroethane, and alcohols.

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Com - pound	mp, °C*	Found, N, %	Empirical formula	Calcu- lated, N, %	Yield, %
IVa	76—77,5	7,5	$ \begin{vmatrix} C_{24}H_{25}N_2O_2\\ C_{30}H_{33}N_2O_2\\ C_{30}H_{22}N_2O_2\\ C_{22}H_{13}N_2O_2 \end{vmatrix} $	7,5	58.8
IVb	Oil [†]	•5,8		6,1	65.5
IVc	157—158,5	•8,0		7,9	78.0
IVd	75—76	8,2		8,2	76,0

TABLE 1. 10-Alkylquindoline-ll-carboxylate Esters

*(IVa, d) from a mixture of ether and light petroleum, and (IVc) from benzene. +Purified by chromatography on plates with a thin layer of alumina, eluent a 4:5 mixture of ethyl methyl ketone and n-hexane, Rf 0.82.

In order to establish the position of the substituent in the δ -benzocarboline system, benzyl 10-benzylquindoline-ll-carboxylate (IVc) was alkylated with methyl iodide at 20°C.



The resulting salt (V) (yield 50%) was soluble in alcohols, but insoluble in ether.

The structures of these quindoline-ll-carboxylic acid derivatives were confirmed by their elemental analyses and their IR and PMR spectra. Comparing the PMR spectra of the methyl and ethyl esters (IIIa, b), identical signals are seen for the aromatic protons and NH (singlet, 9.57 ppm), whereas in the spectrum of the benzyl ester (IVc) this signal is absent, although two singlets for the benzyl CH₂ groups are seen at 5.11 and 5.52 ppm. This is confirmation of the fact that under these conditions, alkylation of the NH group in addition to the ionized carboxyl group takes place.

According to [6], quindoline (II) is obtained on heating the acid (I) at 300°C in paraffin. We have obtained quindoline by decarboxylating (I) at 270°C in diphenyl ether.

The alkylation of quindoline (II) by alkyl halides in solution in ethyl methyl ketone in the presence of powdered potassium hydroxide and a water-binding agent such as calcium oxide has been examined.



VI a $R=C_2H_5$, b $R=p\cdot C_4H_9$, c $R=CH_2(CH_2)_5CH_3$, d $R=CH_2C_6H_5$, e $R=CH_2CH=CH_2$; X=Cl, Br, l

Alkylation of (II) takes place readily at 70°C, being complete in 3-3.5 h. The 10alkylquindolines (VIa-e) were obtained in high yields. This method thus enables alkyl substituents to be successfully introduced into the five-membered ring (in the 10-position) without affecting the more basic nitrogen in the 5-position of the six-membered ring.

The 10-alkylquindolines (VIa-e) are readily soluble in ether, acetone, and chloroform, but they are insoluble in water. Their hydrochlorides (VIIa-e) were obtained by passing gaseous hydrogen chloride into ether or benzene solutions of the appropriate 10-alkylquindoline (VIa-e), and the free bases by treating the hydrochlorides (VIIa-e) with sodium carbonate solution.

The PMR spectra of (VIa-e) and (VIIa-e) are in agreement with the structures of the 10alkylquindolines and their hydrochlorides.

TABLE 2. Yields and Constants of 10-Alkylquindolines (VIb-d) and Their Hydrochlorides (VIIa-e)

Com- pound	mp, ℃ [●]	Found, N, %		Empiric al	Calculated, N, %		Yield,
		ci ·	N	formula	Cl	N	%
VIb VIC VId VIIa VIIb VIIC VIIC VIId	$\begin{array}{c} 92.5 {} 94.5 \\ 77.5 {} 78.5 \\ 147.5 {} 149.5 \\ 266 {} 268 \\ 226 {} 228 \\ 203.5 {} 205.5 \\ 228.5 {} 230.5 \\ 249 {} 251 \end{array}$		10,0 8,4 8,9 8,7 	$\begin{array}{c} C_{19}H_{15}N_2\\ C_{22}H_{24}N_2\\ C_{22}H_{16}N_2\\ C_{17}H_{15}CIN_2\\ C_{19}H_{16}CIN_2\\ C_{22}H_{25}CIN_2\\ C_{22}H_{25}CIN_2\\ C_{22}H_{17}CIN_2\\ C_{18}H_{15}CIN_2 \end{array}$	12.6 11,4 10,1 10,3 12,0	10.2 8.9 9,1 	68,2 67,0 67,4 84,3 87,2 90,5 92,6 91,9

*(VIb-d) were crystallized from ether-light petroleum, and (VIIa-e) from ethanol-ether. **Found, %: C 72.7; H 5.6. Calculated, %: C 72.2; H 5.3.

TABLE 3. PMR Spectral Parameters of 10-Alkylquindolines (VIad) and Their Hydrochlorides (VIIb-d)

Com-	δ, ppm (in CDCl ₃)				
pound	N-CH2	R	CHarom		
VI a VIb VIc VId VIb VII c VII c		1,33 (3H, t, CH ₃) 0.63-2.00 (7H, m, CH ₂ CH ₂ CH ₃) 0,63-2.03 [13H, m, (CH ₂) ₅ CH ₃] 0,70-1.93 (7H, m, CH ₂ CH ₂ CH ₃) 0,63-1.99 [13H, m, (CH ₂) ₅ CH ₃]	7,13 $-$ 8,55 (9H, m) 6,93 $-$ 8.63 (9H, m) 7,18 $-$ 8,60 (9H, m) 6,93 $-$ 8,63 (14H, m) 7,00 $-$ 9,21 (9H, m) 7,00 $-$ 9,15 (9H, m) 6,58 $-$ 8,41 (14H, m)		

*In CF₃COOH.

EXPERIMENTAL

PMR spectra were obtained on a Tesla BS-487C spectrometer (80 MHz), internal standard HMDS, chemical shifts being given on the δ scale. The course of the reactions was followed, and the purity of the products established by TLC on Silufol UV-254 plates (eluent, a 4:5 mixture of ethyl methyl ketone and hexane).

The properties of the compounds obtained are given in Tables 1 and 2, and their PMR spectra in Table 3.

Quindoline Hydrochloride. A mixture of 5.25 g (20 mmoles) of the acid (I) and 53.0 g of diphenyl ether was heated for 6 h at 270°C. The mixture was cooled to 15° C, and 40 ml of light petroleum added. The solid was filtered off, washed with light petroleum (3 × 50 ml), dried, heated in 150 ml of 1 N hydrochloric acid, and filtered. The filtrate was cooled to give 4.0 g (78.4%) of quindoline hydrochloride.

<u>Quindoline (II)</u>. The acid solution obtained as above was neutralized with sodium carbonate to pH 7.5, and extracted with benzene (3×50 ml). The extract was dried with magnesium sulfate, and the solvent removed. Yield, 2.52 g (57.6%); mp 251-252.5°C (from ethanol). Rf 0.61. According to [6], mp 251-252°C.

Ethyl Quindoline-ll-carboxylate (IIIb). A. A mixture of 2.60 g (8.70 mmoles) of quindoline-ll-carboxylic acid hydrochloride (or 2.28 g of (I)), 50 ml of ethanol, and 1.5 ml (28 mmoles) of concentrated sulfuric acid was boiled under reflux for 10 h. The mixture was cooled, 50 ml of water and 100 ml of benzene added, and neutralized with aqueous sodium carbonate to pH 7.5. The benzene layer was separated and dried over magnesium sulfate to give 0.80 g (31.6%) of product, mp 137.5-139°C, R_f 0.87. PMR spectrum (in CDCl₃): 1.45 (3H, t, CH₃), 4.51 (4H, q, CH₂), 7.07-9.05 (8H, m, CH_{arom}), 9.57 ppm (1H, s, NH). Found, %: N 9.4. $C_{18}H_{14}N_2O_2$. Calculated, %: N 9.6.

B. To a solution of 2.60 g (10 mmoles) of (I) in 20 ml of DMF was added 2.24 g (40 mmoles) of potassium hydroxide, 2.24 g (40 mmoles) of calcium oxide, and 10.5 ml (130 mmoles)

of ethyl iodide, and the mixture kept for 15 h. There were then added 60 ml of benzene and 100 ml of water. The benzene layer was separated, washed with water (2×60 ml), and dried over magnesium sulfate. The solvent was removed, and the residue recrystallized from hexane to give 1.10 g (37.9%) of product, mp 136.5-138°C, Rf 0.87.

Butyl Quindoline-11-carboxylate (IIIc). A mixture of 1.5 ml (28 mmoles) of concentrated sulfuric acid, 2.60 g (10 mmoles) of (I), and 40 ml of n-butanol was heated for 6 h with azeo-tropic removal of the water formed. The butanol was distilled off, 40 ml of benzene and 50 ml of water added, and the mixture neutralized with aqueous sodium carbonate to pH 7.5. The benzene layer was dried over magnesium sulfate, and the solvent removed to give 1.30 g (40.9%) of product, mp 143-144°C (from hexane), Rf 0.88.

Methyl Quindoline-ll-carboxylate (IIIa). To a solution of 2.60 g (10 mmoles) of (I) in 20 ml of DMF was added 2.24 g (40 mmoles) of potassium hydroxide, 2.24 g (40 mmoles) of calcium oxide, and 9.7 ml (130 mmoles) of methyl iodide, and the mixture kept for 48 h. To the mixture were then added 60 ml of benzene and 100 ml of water, and the benzene layer was separated, washed with water (2×60 ml), and dried over magnesium sulfate. The solvent was removed, and the residue recrystallized from hexane to give 0.90 g (32.6%) of product, mp 152.5-154°C, Rf 0.87. PMR spectrum (in CDCl₃): 4.10 (3H, s, CH₃), 7.17-9.07 (8H, m, CH_{arom}), 9.57 ppm (1H, s, NH).

Esters of 10-Alkylquindoline-ll-carboxylic Acids (IVa-d). A mixture of 10 mmoles of (I), 120 ml of ethyl methyl ketone, 30 mmoles of potassium hydroxide, and 30 mmoles of calcium oxide was stirred with heating for 30-35 min, then cooled to 10-15°C, and 50 mmoles of the appropriate alkyl halide added gradually (over 1.5 h) with stirring. The reaction was carried out at 65°C for 3-5 h. The mixture was then cooled and filtered, and the solvent and excess alkylating agent removed in a rotary evaporator. The residue was extracted with benzene (2 × 40 ml), and the benzene layer separated, washed with water, and dried over magnesium sulfate. The solution was concentrated to half its volume, and 30 ml of light petroleum or hexane added to the residue. PMR spectrum of (IVc) (in CDCl₃): 5.11 (2H, s, CH₂N), 5.52 (2H, s, CH₂O), 6.97-8.57 ppm (18H, m, CH_{arom}); (IVd) 4.77-6.35 (10 H, m, allyl protons), 7.17-8.55 ppm (8H, m, CH_{arom}).

<u>10-Benzyl-11-benzyloxycarbonylquindolinium Iodide (V).</u> A mixture of 0.50 g (1.2 mmoles) of the benzyl ester (IVc) and 5.0 ml (80 mmoles) of methyl iodide was kept at 20°C for 24 h. Excess methyl iodide was distilled off, and the residual crystalline solid dissolved in ethanol and treated with ether (10 ml) until the product had been completely precipitated. Yield, 45-50%, orange crystals, mp 177-179°C. Found, %: C 63.4; H 4.6; N 4.8. C₃₁H₂₅IN₂O₂. Calculated, %: C 63.7; H 4.3; N 4.8.

<u>10-Alkylquindoline Hydrochlorides (VIIa-e)</u>. A mixture of 6.3 mmoles of quindoline hydrochloride, 25 mmoles of powdered potassium hydroxide, 25 mmoles of calcium oxide, and 50 ml of ethyl methyl ketone was heated for 1.5 h at 65°C. The mixture was cooled to 10°C, 32 mmoles of the alkyl halide added gradually over 1 h, and the mixture kept at 65°C for 6-6.5 h. It was then cooled and filtered, and the filtrate evaporated in a rotary evaporator until all the solvent and excess alkyl halide had been removed. The residue was extracted with ether (2×50 ml), and the ether layer separated, washed with water (2×100 ml), and dried over magnesium sulfate. It was then filtered, and a stream of hydrogen chloride passed through the solution. The yellow, pulverulent hydrochloride which separated was filtered off and washed thoroughly with ether.

<u>10-Alkylquindolines (VIb-d)</u>. The hydrochloride (VIIb-d) (10 mmoles) was shaken with 5% aqueous sodium carbonate, and extracted with ether $(2 \times 60 \text{ ml})$. The organic layer was separated, and dried over magnesium sulfate. The ether was removed, and the residue recrystallized from light petroleum (or a mixture of ether and hexane).

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