The Pfitzinger Reaction with Unsymmetrical Ketones

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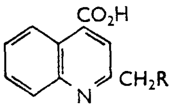
The ratios of the products obtained from the Pfitzinger reaction with a series of dialkyl, alkyl arylalkyl, and alkyl aryloxymethylketones have been determined. These results, and the Friedlander reaction on ethyl methyl ketone, show that steric effects have a marked influence on the product ratio from dialkyl ketones, but that with compounds of similar steric requirements in the aromatic series electronic effects are also important. Analysis of the u.v. and n.m.r. spectra of the cinchoninic acids shows that in the 3-unsubstituted compounds the carboxy-group is coplanar with the aromatic rings even when the ring is protonated, but that the carboxy-group of the 3-substituted compounds is very much out of plane except where the substituent is a hydroxy-group. Hückel molecular orbital calculations of π-electron energy and other quantities in the intermediate anions have been carried out.

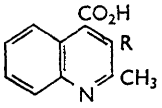
In the Pfitzinger reaction of isatin and the ketones (I) condensation can occur through either the methyl or the methylene group, leading to the 2-substituted (II) and 2,3-disubstituted (III) cinchoninic acids respectively. With ethyl methyl ketone, solely (III; R = Me)[1,2] and a mixture of (II; R = Me) and (III; R = Me) have been claimed to be formed,[3] while with higher homologues only (II) is reported.[4] With aryloxy-ketones (I; R = *O*-aryl),[5] alkoxy-ketones (I; R = OEt *etc.*),[6] and ethyl acetoacetate [7] only condensation through the methylene group is reported.

$CH_3{\cdot}CO{\cdot}CH_2R$

(I)



(II)



(III)

Recently we used the Pfitzinger reaction during the unambiguous synthesis of 2- and 4-hydroxymethylquinolines,[8] and it became apparent that the above information was unreliable (*cf.* ref. 9) and the reaction was therefore reinvestigated (*a*) to determine more accurately the ratio of isomers (II) and (III) formed from unsymmetrical ketones and (*b*) to see whether Hückel molecular orbital theory provides an explanation of the difference in behaviour of the various systems.

After being heated for 15 hr. at 100°, mixtures of the ketone (I) (2 mol.), isatin (1 mol.), and 33% (w/v) aqueous potassium hydroxide (3 mol.) were neutralised, and the product was separated and investigated by ^1H n.m.r. spectroscopy (Table 1). Since the quinolines (II) and (III) (in trifluoroacetic acid) contain either a methylene group (variable τ value) or a methyl group (signal near τ 7·0) estimation of the mixtures by direct integration was possible.

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[1] W. Pfitzinger, *J. prakt. Chem.*, 1897 [2], **56**, 283.

[2] Ng. Ph. Buu-Hoï, *J. Chem. Soc.*, 1946, 795.

[3] J. von Braun, W. Gmelin, and A. Schultheiss, *Ber.*, 1923, **56**, 1338.

[4] Ng. Ph. Buu-Hoï and R. Royer, *J. Chem. Soc.*, 1948, 106.

[5] P. K. Calaway and H. R. Henze, *J. Amer. Chem. Soc.*, 1939, **61**, 1355; A. M. Dowell, H. S. McCullough, and P. K. Calaway, *ibid.*, 1948, **70**, 226; J. A. Knight, H. K. Porter, and P. K. Calaway, *ibid.*, 1944, **66**, 1893.

[6] (*a*) L. B. Cross and H. R. Henze, *J. Amer. Chem. Soc.*, 1939, **61**, 2730; (*b*) S. D. Lesesne and H. R. Henze, *ibid.*, 1942, **64**, 1897.

[7] W. Pfitzinger, *J. prakt. Chem.*, 1897 [2], **56**, 316.

[8] M. H. Palmer and P. S. McIntyre, *Tetrahedron Letters*, 1968, 2147.

[9] R. C. Elderfield, 'Heterocyclic Compounds,' Wiley, New York, 1952, vol. 4, pp. 49, 54.

TABLE 1

Pfitzinger reaction product ratios (%) *

R in (I)	Me (a)	Et (b)	Pr^i (c)	C_6H_5 (d)	4-MeO·C_6H_4 (e)	4-NO_2·C_6H_4 (f)
(II)	50	95	100	38	40	0
(III)	50	5	0	62	60	100

R in (I)	HO (g)	C_6H_5O (h)	4-MeO·C_6H_4O (i)	4-NO_2·C_6H_4O (j)
(II)	0	38	29	0 †
(III)	100	62	71	0 †

* Determined by ^1H n.m.r. spectroscopy in CF_3·CO_2H as solvent. All results ±3%, except where only one isomer detected. † Only 4-nitrophenol and isatin isolated.

The physical constants and spectra of the products are given in Table 2.

3-Hydroxy-2-methylcinchoninic acid (III; R = OH) was readily isolated from the reaction with hydroxyacetone. In the reaction with 4-nitrophenoxyacetone (Ij) only 4-nitrophenol and isatin were isolated; thus nucleophilic displacement of the substituent group in the substituted acetone is more rapid than the cyclization sequence; there was no indication of the fate of the ketone in this reaction.

TABLE 2

Cinchoninic acids

			^1H N.m.r. spectrum (τ) [a]		
R in (II)	M.p.[b]	2-Substnt.	3-H	5-H	6-H, 7-H, 8-H
Me	171—172° (d) [c]	6·50 (CH_2) 8·30 (CH_3)	1·47	0·90	1·60—2·00
Et	155—156 (d) [d]	6·50 (α-CH_2) 7·85 (β-CH_2) 8·77 (CH_3)	1·45	0·90	1·60—2·00
$CHMe_2$	192—193 (d)	6·71 (CH_2) 7·58 (CH) 8·80 (CH_3)	1·56	0·93	1·60—2·00
C_6H_5	220 (d) [f]	5·22 (CH_2) 2·50 (C_6H_5)	1·43	0·80	1·60—2·00
4-MeO·C_6H_4 *	207—208 (d) [g]	5·20 (CH_2) 2·40—2·80 (C_6H_4) 5·90 (CH_3O)	1·60	0·90	1·60—1·80
C_6H_5O	196 (d) [h]	4·13 (CH_2) 2·40—2·70 (C_6H_5)	1·30	0·80	1·40—2·00
4-MeO·C_6H_4O *	164—165 (d) [i]	4·18 (CH_2) 2·80—3·00 (C_6H_4) 5·98 (CH_3O)	1·35	0·83	1·60—2·00

R in (III)	M.p.	2-Me	3-Substnt. (R)	5-H, 6-H, 7-H, 8-H
Me	309—310° (d) [j]	6·87	7·26 (CH_3)	1·60—2·00
C_6H_5	312 (d) [k]	7·06	2·20—2·70 (C_6H_5)	1·60—2·0
4-NO_2·C_6H_4 *..............	222—223 (d) [l]	7·00	2·30—2·60 (C_6H_4)	1·60—1·90
4-MeO·C_6H_4 *	289—290 (d) [m]	7·40	2·40—2·80 (C_6H_4), 5·93 (CH_3O)	1·60—1·70
OH	242 (d) [n]	6·87	—	0·8 (5-H) 1·60—2·00
C_6H_5O	259—260 (d) [o]	7·00	2·30—2·90 (C_6H_5)	1·60—2·00
4-MeO·C_6H_4O	213—214 (d) [p]	7·00	2·80—3·00 (C_6H_4) 6·00 (CH_3O)	1·60—2·00

* New compound; analysis given in footnote.

[a] In CF_3·CO_2H containing $Si(CH_3)_4$. [b] Uncorrected. [c] O. Doebner (*Annalen*, 1887, **242**, 265) gives m.p. 173°. [d] Ref. 4 gives m.p. 156°. [e] Ref. 4 gives m.p. 192°. [f] W. Borsche and O. Vorbach (*Annalen*, 1938, **537**, 22) give m.p. 220°. [g] Found: C, 73·7; H, 5·1; N, 4·7. $C_{18}H_{15}NO_3$ requires C, 73·7; H, 5·1; N, 4·7%. [h] N. Okuda (*J. Pharm. Soc., Japan*, 1951, **71**, 1275) gives m.p. 196°. [i] Found: C, 69·7; H, 4·9; N, 4·5. $C_{18}H_{15}NO_4$ requires C, 69·9; H, 4·8; N, 4·5%. [j] Ref. 4 gives m.p. 310°. [k] W. Borsche and O. Vorbach (*Annalen*, 1938, **537**, 22) give m.p. 312°. [l] Found: C, 66·1; H, 3·8; N, 9·0. $C_{17}H_{12}N_2O_4$ requires C, 66·2; H, 3·9; N, 9·1%. [m] Found: C, 73·6; H, 5·1; N, 4·8. $C_{18}H_{15}NO_3$ requires C, 73·7; H, 5·1; N, 4·7%. [n] Ref. 6*a* gives m.p. 242—244°. [o] N. Okuda (*J. Pharm. Soc. Japan*, 1957, **71**, 1275) gives m.p. 259—260°. [p] R. L. Sublett and P. K. Calaway (*J. Amer. Chem. Soc.*, 1948, **70**, 674) give m.p. 215°.

In view of our recent work on the Fischer indole synthesis with unsymmetrical ketones,[10] where the product ratio varies with the acid strength, the Pfitzinger reaction with ethyl methyl ketone was studied over the range 15—50% (w/v) potassium hydroxide concentration. No significant change in product ratio (II : III) was observed, and it seems unlikely that any should be expected unless, for example, dianion formation occurs in the enamine side-chain. With this in mind, attempts were made to condense the dianion[11] of pentane-2,4-dione with the sodium salt of isatinic acid in liquid ammonia containing 3 mol. of sodamide. After a reaction for 3 hr. most of the isatin was recovered, and the remaining product was a complex mixture (^1H n.m.r. spectrum *etc.*). It was concluded that condensation of the terminal position of the dianion with the carbonyl group of the sodium isatinate had not occurred substantially, if at all. Under the normal Pfitzinger reaction conditions the sole product from pentane-2,4-dione was confirmed (*cf.* ref. 12) to be 3-acetyl-2-methylcinchoninic acid (III; R = Ac).

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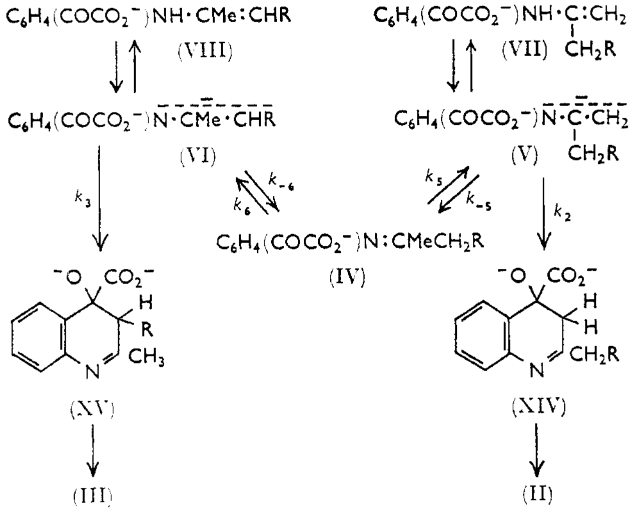
[10] M. H. Palmer and P. S. McIntyre, *J. Chem. Soc.* (*B*), 1969, 446.

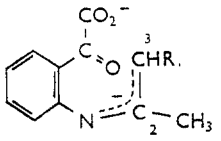
[11] C. R. Hauser and T. M. Harris, *J. Amer. Chem. Soc.*, 1958, **80**, 6360.

[12] Gj. Stevanovic, M. Pavicic-Woss, Lj. Lorenc, and M. Lj. Mihailovic, *Tetrahedron*, 1959, **6**, 97.

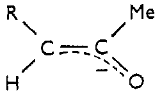
DISCUSSION

Comparison of our results with those of earlier investigations [1-6] shows that the major product was correctly identified, but that substantial amounts of the second isomer were formed in most cases except those of the dialkyl ketones (Ib, Ic, Ig). It is probable [13] that the Pfitzinger reaction occurs by the following stages: (*a*) base-catalysed cleavage of the isatin to the isatinic acid anion, (*b*) condensation between the amino-group and the ketonic carbonyl group, (*c*) base-catalysed removal of a proton from the α-position of the Schiff base (IV), and (*d*) cyclization of the anions (V) or (VI) by carbonyl condensation. A study of molecular models shows that cyclization can most readily occur if both the carbonyl and carbanionoid centres are out of plane with respect to the aromatic ring, and further that steric repulsion of the carboxylate and carbanionoid centres is less in the conformation (IX). Under these conditions there is little through-conjugation between the two systems (see below). In the following discussion it is convenient to separate steric from electronic effects in the first instance.

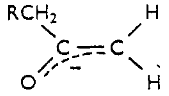




(IX)



(X)



(XI)

Steric Effects.—In the Pfitzinger reactions of the dialkyl ketones (Ia, Ib, Ic) the gross difference in product ratio from the methyl and ethyl and isopropyl compounds is indicative of steric control; * [2,4] thus the reaction rates for (V) ⟶ (II) will not be substantially different for R = Me from R = Et; but for the reaction (VI) ⟶ (III), models show that during rotation about the αβ-bond (XII), the γ-methyl group strongly interferes with both the α′-methyl group and the carboxylate anion; thus the reaction (VI) ⟶ (III) should be much slower for R = Me, as appears to be the case from the isomer ratio (II and III) obtained in these reactions (Table 3).

TABLE 3

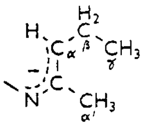
Ethyl esters of (II)

^1H N.m.r. spectrum (τ) [a]

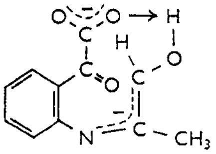
R =	2-Substnt.	3-H	5-H [c]	6-H, 7-H [c]	8-H [c]	4-Substnt. [b]
C_6H_5	5·68 (CH_2) 2·78 (C_6H_5)	2·3	1·35	2·45	1·85	5·55 (CH_2) 8·65 (CH_3)
4-MeO·C_6H_4...	5·72 (CH_2) 2·75, 3·18 (C_6H_4) 6·33 (OCH_3)	2·28	1·3	2·40	1·85	5·58 (CH_2) 8·63 (CH_3)
C_6H_5O	4·67 (CH_2) 2·65—3·2 (C_6H_5)	1·85	1·23	2·38	1·88	5·55 (CH_2) 8·60 (CH_3)
4-MeO·C_6H_4O	4·68 (CH_2) 2·85—3·3 (C_6H_4)	1·88	1·28	2·36	1·93	5·52 (CH_2) 8·58 (CH_3)

[a] In $CDCl_3$. [b] R′ of CO_2R'. [c] In ABXY spectra of the disubstituted benzene-ring type, a common feature is elements of symmetry in the spectrum, *i.e.*, X and Y lines are mirror images, and the AB part has a plane of symmetry. This occurs when the coupling constants $J_{AX} = J_{AY}$ *etc.* We have not applied a complete analysis of these spectra, so that the figures for 6-H and 7-H represent their mean position.

In the Friedlander reaction with ethyl methyl ketone and *o*-aminobenzaldehyde, the ratio of 2,3-dimethyl- to 2-ethyl-quinolines was 85% : 15%; *i.e.*, higher than in the corresponding Pfitzinger reaction (only the former compound has been claimed [14] previously). This is probably a steric effect of the above type, but further investigation with *o*-amino-ketones failed owing to the instability of these compounds to base. The result of the Pfitzinger reaction on hydroxyacetone (Ig) is explicable in terms of formation of the longest conjugated anion (see molecular orbital interpretation below), since the steric effects of the reacting molecule (VI; R = OH) are small (and similar to that in the reaction with butan-2-one). Although hydrogen bonding may also assist the product orientation, neither the nitrogen nor the carboxy-group (*e.g.*, XIII) have orbitals lying in directions suitable for efficient overlap.



(XII)



(XIII)

The steric hindrance to cyclization of the aryl compounds (VI; R = C_6H_5, 4-C_6H_4·NO_2, and 4-C_6H_4·OCH_3) is similar to that in the propenyl compound (VI;

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* The [N–C–C]⁻ and [O–C–C]⁻ systems are isoelectronic; the equilibrium concentrations of the enolate anions (X) and (XI) for R being an unbranched alkyl group are approximately equal, while for R being a branched alkyl group the less highly substituted anion (XI) predominates. These are clearly electronic effects (H. O. House and V. Kramar, *J. Org. Chem.*, 1963, **28**, 3362).

[13] H. G. Lindwall and J. S. MacLennan, *J. Amer. Chem. Soc.*, 1932, **54**, 4739.

[14] J. Eliasberg and P. Friedlander, *Ber.*, 1892, **25**, 1752.

R = Et), and this is no doubt responsible for the relatively high proportion of the product from the unconjugated anion (V; R = C_6H_5, 4-C_6H_4·NO_2, and 4-C_6H_4·OMe). A similar situation applies with the aryloxy-ketones (Ih, Ii) where steric interaction between the aryl group and the α′-methyl group (*cf.* XII) or carboxylate anion occurs if the $2p_z$ electrons of the oxygen atom are fully conjugated with both the aryl and enamine anions (VI) (see below also).

Electronic Effects.—In the following discussion we have used the unrefined Hückel molecular orbital approach,[15] with overlap neglected to determine (*a*) the total π-electron energy of the reacting anions in which the charge is considered to be localised in the $(\text{-N-CMe-CHR})^-$ or $[\text{-N-C}(CH_2R)\text{-}CH_2]^-$ parts of the molecule [this is justified since a consideration of molecular models (see above) shows that these parts cannot become coplanar with the rest of the molecule when cyclization is occurring]; (*b*) π-electron densities at the carbon atom which undergoes cyclization [and which becomes C(3) of the quinoline]; and (*c*) polarisability of this carbon atom. Calculations were performed with the computer programme CHUC (for which we are indebted to C. W. Haigh) on an IBM 360/67 computer. The Coulomb and resonance integrals, similar to those generally recommended, for oxygen (α_O), nitrogen (α_N), the C–O bond (β_{CO}) and the C–N bond (β_{CN}) are given by $\alpha_O = \alpha_C + 2\beta_{CC}$, $\alpha_N = \alpha_C + 0{\cdot}5\beta_{CC}$, $\beta_{CO} = 0{\cdot}7\beta_{CC}$ and $\beta_{CN} = \beta_{CC}$, where β_{CC} is the resonance integral for the C–C bonds. These parameters lead to the total π-electron energies, charge densities, and polarisabilities shown in Table 4.

TABLE 4

Total π-electron energy for the cyclization of the anions (V) and (VI)

R =	H	OMe (or OH)	$-C_6H_5$	$-C_6H_4 \cdot OCH_3$	$-O \cdot C_6H_5$	$-O \cdot C_6H_4 \cdot OCH_3$
$E^{II}{}_V$ [b]	3·628	3·628	11·62	15·718	15·718	19·928
$E^{II}{}_{VI}$	3·628	7·680	12·1	16·269	15·879	20·025
$-q_{VI}$ [c]	1·38	1·32	1·30	1·30	1·32	1·32
π_{VI} [d]	0·510	0·504	0·399	0·400	0·500	0·494

[a] Excluding the contributions from the $C_6H_4(COCO_2)$ system. [b] In units of β_{CC}. [c] Charge density. [d] Polarisability in units of $\beta_{CC}{}^{-1}$.

Conclusions.—It seems probable that under basic conditions, as in the present work, the Schiff base (IV) rapidly forms an anion (V) or (VI), since attempts to isolate Schiff bases of ketones from direct reaction of amines with ketones generally lead to a quinoline directly (presumably by further condensation of the Schiff-base anion with more ketone and then cyclization).

The overall rate equation for quinoline formation, based upon stationary-state concentrations of the anions (V) and (VI) which are high with respect to that of the Schiff base, is given by equation (1). This equation can be simplified considerably in two extreme cases: (*a*) if the rate-controlling step is ionisation of the Schiff base to give (V) and (VI), and if cyclization is much faster than re-protonation of the anion, then the product ratio ($R_{II} : R_{III}$) is given by equation (2). Whilst the second proviso is possible, owing to the juxtaposition of the two reacting groups, the results obtained with the alkyl compounds [where the ratio of ionisation rates of (IV) to (V) and (VI) is likely to be near unity] do not support such a mechanism. It is noteworthy that only the total π-electron energy is relevant to such a mechanism since the rates of reaction (k_5 and k_6) are given by equation (3) where ΔE_π is the difference in π-electron energies for (V) and (VI). In all the reactions with aromatic substituents (R) the π-electron energy is higher for the long conjugated anion (VI).

$$\frac{R_{II}}{R_{III}} = \frac{k_5}{k_6} \cdot \frac{k_2}{k_3} \cdot \frac{k_3 + k_{-6}}{k_2 + k_{-5}} \quad (1)$$

$$\frac{R_{II}}{R_{III}} = \frac{k_5}{k_6} \quad (2)$$

$$-\Delta E_\pi = \boldsymbol{R}T \log_e \frac{k_6}{k_5} \quad (3)$$

$$\frac{R_{II}}{R_{III}} = \frac{k_5}{k_6} \cdot \frac{k_{-6}}{k_{-5}} \cdot \frac{k_2}{k_3} = \frac{Kk_2}{k_3} \quad (4)$$

A more probable explanation is (*b*), that the rate-determining step is cyclization to the quinolines (XIV) and (XV); here equation (1) simplifies to equation (4), where *K* is the ratio of the equilibrium constants for the Schiff base ionisations. For the ketone (I; R = Ph) the equilibrium concentrations of the anions (X; R = Ph) and (XI; R = Ph) are >98% and <2% respectively; the ratio for the enamine anions [(V) and (VII) where R = Ph and C_6H_4·OMe] could be similar and that for the 4-nitrophenyl compound relatively higher, since the π-electron energies are favourable to the anions (VI) and their polarisabilities are lower than that of the unconjugated species (V); this will have the effect of reducing their rates of reprotonation ($k_{-6} < k_{-5}$) as well as cyclization. The observed ratios of quinolines (II) and (III), favouring the reaction through the anion (VI; R = Ph, C_6H_4·OMe, and C_6H_4·NO_2) is thus interpreted in terms of a favourable equilibrium constant (*K*) partly offset by low reactivity and steric retardation reducing k_3.

There are no data for equilibrium concentrations of the anions of phenoxyacetone, but the calculated π-electron energies and polarisabilities suggest that the long conjugated anions (X and VI; R = OPh and O·C_6H_4·OMe) will predominate but with lower proportions than the phenyl compounds above. We have

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[15] A. Streitwieser, 'Molecular Orbital Theory for Organic Chemists,' Wiley, New York, 1962, pp. 15, 117 *et seq.*

no explanation of the difference in behaviour of the phenoxy- and 4-methoxyphenoxy-compounds (I).

For the ketones (I; R = Bu^n and Pr^i) the proportions of terminal enolate anion (XI), as determined by deuterium quenching, are 58% and 82% respectively; the figure for (I; R = Et) is probably similar to the former. The observed proportions of the quinolines (II) (R = Et and Pr^i) are higher than these figures showing the steric retardation of the reaction (VI) ⟶ (III) (above).

Spectra of the Cinchoninic Acids and Esters.—The ^{1}H n.m.r. spectra of the 3-unsubstituted acids (II) in trifluoroacetic acid show absorption near τ 0·9, which from its multiplicity and general form is the X part of an ABCX spectrum,[16] and is thus due to either the 5- or the 8-proton. The corresponding ethyl esters of (II) show multiplets near τ 1·3 and 1·8 which are clearly the X and Y parts of an ABXY spectrum;[17] these results are consistent with the 5-H lying at about τ 1·3 and 0·9 in neutral and acidic media respectively, and with the 8-H at τ 1·8 and above in the same solutions; the magnetic anisotropy which is largely responsible [18] for the downfield position of the 8-H is removed on protonation. Final confirmation of these assignments comes from the Pfitzinger reaction products with ethyl methyl ketone and 5-chloroisatin; neither of the products (*cf.* II and III) showed an absorption near τ 0·9. The observation that the 5-H signal is at least 0·7 p.p.m. upfield in the spectra of the 3-substituted acids (III) shows that the carboxy-group must be coplanar in the 3-unsubstituted compound even when protonated, and out of plane in the 3-substituted compounds. The sole exception is the 3-hydroxy-acid (III; R = OH) and this can be ascribed to hydrogen bonding between the substituents enforcing coplanarity; a similar effect on the chemical shift of *peri*-protons has been observed with 2-hydroxynaphthoic acid derivatives and related ring systems,[19] and polycyclic ketones.[20]

TABLE 5

Ultraviolet spectrum of 2-ethyl- and 2,3-dimethyl-cinchoninic acids

	(II; R = Me)				(III; R = Me)			
$\lambda_{max.}$ (mμ) ...	209	231	294	315	214	230	286	316
log ε	4·86	4·82	4·66	4·61	4·88	4·72	4·55	4·51

The u.v. spectra (Table 5) of (II; R = Me) and (III; R = Me) show a reduction in intensity (20%) in the latter case as expected for out-of-plane twisting of the carboxy-group. A further feature is the smaller difference in wavelength between the *p*- and α-bands [21] in the unhindered compound; a similar feature appears for quinoline-3-carboxylic acid when compared with its 4-methyl homologue.[22]

EXPERIMENTAL

^{1}H N.m.r. spectra were obtained with a Perkin-Elmer R10 instrument at 60 Mc./sec. The ketones were either commercial samples, purified where necessary, or prepared by published methods.

Typical Pfitzinger Reaction Procedure.—The ketone (0·52 mole) was added to a solution of isatin (5 g., 0·035 mole) in 33% (w/v) aqueous potassium hydroxide (30 g.) and the mixture boiled for 16 hr. After treatment with ice (100 g.), extraction of non-alkali-soluble material, and acidification to pH 6—7 (with acetic acid), the product was filtered off, dried, and analysed by ^{1}H n.m.r. spectroscopy, by use particularly of the $-CH_2-$ and $-CH_3$ resonances [(II) and (III) respectively]. Similar examination of the aqueous phase showed that no product remained therein; yields were in the range 60—85% based on the isatin.

Partial Esterification of the Mixtures.—General procedure. The cinchoninic acid mixture [(II) + (III), 4 g.] was boiled with ethanol (20 ml.) and sulphuric acid (*d* 1·84, 10 ml.) for 0·5 hr. After treatment with ice (100 g.) and basification with sodium hydroxide, the basic material was extracted with ether. Evaporation of the dried ($MgSO_4$) extracts gave the ethyl ester of the 2-substituted cinchoninic acids, as shown by the absence of CH_3 absorption (III) near τ 7 and the presence of a singlet near τ 1·5 [3-H of (II)].

The esters were hydrolysed with boiling 20% (w/v) aqueous potassium hydroxide to give the pure 2-substituted cinchoninic acids (II), whose physical constants are given in Table 2.

*Attempted Reaction of Pentane-*2,4-*dione Dianion with Sodium Isatinate.*—Sodium isatinate (0·1 mole), prepared by evaporation to dryness of a solution of isatin in aqueous sodium hydroxide, was added to the disodium salt [15] of pentane-2,4-dione (0·1 mole) in liquid ammonia containing sodamide (0·3 mole). After vigorous stirring for 3 hr., evaporation and neutralisation gave a product whose spectra indicated a complex mixture, in which the main component was isatin.

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[16] J. W. Emsley, J. Feeney, and L. H. Sutcliffe, 'High Resolution Nuclear Magnetic Resonance Spectroscopy,' Pergamon Press, Oxford, 1965, p. 423.

[17] N. V. Riggs, *Austral. J. Chem.*, 1963, **16**, 521.

[18] C. W. Haigh, M. H. Palmer, B. Semple, *J. Chem. Soc.*, 1965, 6004.

[19] M. H. Palmer and N. M. Scollick, *J. Chem. Soc.* (*B*), 1968, 1353.

[20] R. H. Martin, N. Defay, and F. Geerts-Evrard, *Tetrahedron*, 1964, **20**, 1505.

[21] E. Clar, 'Aromatische Kohlenwasserstoffe,' Springer, Berlin, 1952.

[22] E. A. Fehnel, J. A. Deyrup, and M. B. Davidson, *J. Org. Chem.*, 1958, **23**, 1996.