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ORIENTATION EFFECTS IN THE SYNTHESIS OF QUINOLINE DERIVATIVES

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Abstract—The ratio of isomers obtained in the synthesis of quinoline derivatives commencing from *m*-toluidine and 3,4-dimethylaniline has been studied. Introduction of additional 2- and/or 3-alkyl substituents into the heterocyclic ring has little effect, whilst introduction of a 4-alkyl substituent, either alone or in combination with 2- and/or 3-alkyl groups, causes the proportion of the 5- or 5,6-isomer to fall to zero. In the Beyer synthesis with butanone, 3-condensation predominates, although 1-condensation does occur to a small extent. The quinoline products have been carefully analysed by GLC, NMR and fractional crystallisation techniques, the value of *peri*-substituent effects in the interpretation of ^1H NMR spectra is propounded.

Unlike the detailed studies[1,2] of the orientation effects in the Skraup reaction with *m*-substituted- and 3,4-disubstituted aniline derivatives to produce 5- and 7-substituted and 5,6- and 6,7-disubstituted-quinolines respectively, a comprehensive systematic investigation into similar effects to produce quinolines substituted additionally in the heterocyclic ring has not been undertaken. Although a number of isolated studies have been reported, much of the work dates from the very early period before reliable techniques for the separation and identification of the isomeric quinoline products became available, hence the results need to be viewed with caution. As an illustration, the Skraup reaction with *m*-ethylaniline, which was originally claimed[3,4] to produce 7-ethylquinoline only, does give rise to a mixture of products as a recent re-investigation, using GLC and NMR techniques, has shown.[5] A summary of the work reported to date, for reactions commencing with *m*-toluidine and 3,4-dimethylaniline, is given in Table 1.

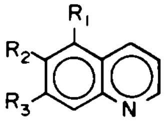
It is evident from Table 1 that few data concerning the precise isomer ratios for compounds substituted in the heterocyclic ring are available. Certain workers have commented that one particular isomer was present in greater proportion[3,7] whilst in other cases the product was assigned as a single isomer, without consideration of the possible presence of the alternative isomer.[3,6,8,14,15] In other cases the presence of the second isomer was considered unlikely, however, no experimental evidence was presented to substantiate this assumption, other than the sharp melting point of the product or of its picrate derivative.[3,9,10] Harz[11] concluded that the Doebner-von Miller reaction of *m*-toluidine and propionaldehyde could lead to a mixture of products, however, since the picrate derivative gave a sharp m.p., the product was considered as a single substance of unknown identity. Berend[12] and Merz[13] performed the Doebner-von Miller reaction with paraldehyde and 3,4-dimethylaniline to obtain a product referred to as "dimethylquinaldine", the compound was later listed in "Beilsteins Handbuch" as 2,5,6- and/or 2,6,7-trimethylquinoline.[17]

In view of the lack of conclusive experimental data on the isomer ratios obtained in the above syntheses, together with the doubts that exist concerning the possible presence of one or two products in certain cases, these reactions have been re-investigated under controlled experimental conditions, since it is not unusual for the recorded properties of a compound to vary by more than reasonable experimental error when determined by different investigators. To facilitate comparison of results the additional substitutents introduced into the heterocyclic ring were generally Me groups, except that for preparative convenience propionaldehyde was used as a reactant in the Doebner-von Miller synthesis to provide the 2-ethyl-3-methyl-substituted quinoline.[11,18] Alternative preparations of the 2,3-dimethylquinolines are less readily performed.[19] The syntheses and reactants employed are summarised in Table 2, and the results obtained are shown in Table 3.

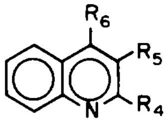
Two experimental difficulties were encountered in this study. Commercial samples of 3-methylpentan-2,4-dione **5** were generally found to be contaminated with pentan-2,4-dione, a synthetic sample[21] was similarly impure. An impure sample of **5** was rigorously purified *via* the copper salt; the quinoline products obtained using this purified material then exhibited no signal for the H-3 proton in the NMR spectrum. The physical properties of samples of 2,3,4-trimethylquinoline and of **2j** thus obtained were considerably different when compared with those obtained by earlier workers.[10,22] It is considered that these latter samples must have been obtained from impure samples of **5**. Such discrepancies were not experienced during the synthesis of **4j**, however, since the earlier preparation of this compound involved a Skraup reaction commencing from 3-methylpent-3-ene-2-one.[16]

For the preparation of 3,4-dimethylquinoline derivatives, the Beyer synthesis was used, with butanone **6a** as reactant. This asymmetric ketone, in which both alkyl groups contain α-H atoms, could lead to two possible reaction pathways. Ardashev and Tertov[23] have reported that reaction of aniline with **6a** gave 3,4-dimethylquinoline **7a** as the predominant product; it was claimed that the alternative product, 4-ethylquinoline **7b**, was also formed, however, this was not supported by any confirmatory evidence, other than that repeated crystallisation of the crude **7a** product removed the **7b** impurity. The predominance of the 3,4-disubstituted product is consistent with the known interaction of ketones of the type **6** with aldehydes in the aldol condensation, since in acid medium all methyl n-alkyl ketones have been reported to participate in 3-condensation.[24,25]

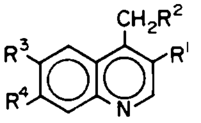
1 2 3 R = alkyl, aryl or H
$CH_3COCHRR'$ R' = alkyl or aryl
6 a: R = H, R' = CH_3



1 $R_1 = CH_3$ $R_2 = R_3 = H$
2 $R_3 = CH_3$ $R_1 = R_2 = H$
3 $R_1 = R_2 = CH_3$ $R_3 = H$
4 $R_2 = R_3 = CH_3$ $R_1 = H$



a $R_4 = R_5 = R_6 = H$
b $R_4 = CH_3$ $R_5 = R_6 = H$
c $R_5 = CH_3$ $R_4 = R_6 = H$
d $R_6 = CH_3$ $R_4 = R_5 = H$
e $R_4 = R_5 = CH_3$ $R_6 = H$
f $R_4 = C_2H_5$ $R_5 = CH_3$ $R_6 = H$
g $R_4 = R_6 = CH_3$ $R_5 = H$
h $R_5 = R_6 = CH_3$ $R_4 = H$
j $R_4 = R_5 = R_6 = CH_3$



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a $R^1 = CH_3$ $R^2 = R^3 = R^4 = H$
b $R^2 = CH_3$ $R^1 = R^3 = R^4 = H$
c $R^2 = R^3 = R^4 = CH_3$ $R^1 = H$

Table 1. Orientation effects in quinoline syntheses

Isomeric alkylquinolines synthesised	Composition of product (%) (a)	Date	Ref.
1b / 2b	2b (b)	1884	6
	1b (S) 2b (G)	1942	3
1c / 2c	1c (10) 2c (90) (c)	1942	3
	1c (S) 2c (G)	1943	7
1d / 2d	2d (b)	1913	8
	2d (d)	1942	3
1e / 2e	-	-	-
1f / 2f	? (e)	1885	11
1g / 2g	2g (d)	1950	9
1h / 2h	2h (b)	1942	3
1j / 2j	2j (d)	1946	10
3b / 4b	- (f)	1884	12,13
3c / 4c	-	-	-
3d / 4d	4d (b)	1965	14
3e / 4e	-	-	-
3f / 4f	-	-	-
3g / 4g	4g (b)	1958	15
3h / 4h	4h (d)	1968	16
3j / 4j	4j (d)	1963	16

a - G - Greater, S - smaller.

b - Product considered as isomer shown, no mention made of other isomer.

c - Tentative result.

d - Product considered to be substantially the isomer shown, possibility of formation of other isomer considered, but thought to be absent.

e - Possibility of isomeric products considered. Product thought to be a single compound, identity not established.

f - Possibility of isomeric products not considered.

Table 2. Synthesis of quinoline derivatives

Heterocyclic ring Substituents present	Synthesis and reactants used	Literature references (a) m-toluidine	Literature references (a) 3,4-dimethylaniline
nil	Skraup (glycerol)	1-3	2,3,20
2-methyl-	Doebner - von Miller (acetaldehyde)	3,6	12,13
3-methyl-	von Miller - Kinkelin (propionaldehyde/paraformaldehyde)	3,7	-
4-methyl-	(i) Skraup (methyl vinyl ketone) (ii) Knorr (ethylacetoacetate)	3,8	14
2-ethyl-3-methyl-	Doebner - von Miller (propionaldehyde)	11	-
2,4-dimethyl-	Combes (pentan-2,4-dione)	9	15
3,4-dimethyl-	Beyer (butanone, paraformaldehyde)	3	16
2,3,4-trimethyl-	Combes (3-methylpentan-2,4-dione)	10	16

a - References are given to reactions commencing from the amines indicated to give the appropriate quinoline products. The preparative method used was not necessarily the same as in this work.

Table 3. Isomer ratios of 5-/7-methyl- and 5,6-/6,7-dimethyl quinoline derivatives

Heterocyclic ring substituents	Composition of mixture (%) (a) 5-Me	7-Me	Composition of mixture (%) (a) $5,6-Me_2$	$6,7-Me_2$
nil	30	70	25	75
2-Me	30	70	29	71
3-Me	27	73	28	72
4-Me (via Knorr)	0	100	1 (b)	99
4-Me (via Skraup)	0	100	1 (b)	99
2-ethyl-3-Me	27	73	21	79 (c)
$2,4-Me_2$	0	100	0	100
$3,4-Me_2$	0	100	0	100
$2,3,4-Me_3$	0	100	0	100
4-ethyl				excess (c)

a - by NMR and GLC.

b - by GLC (see discussion).

c - by NMR only.

In order to assess whether any 1-condensation does occur in the Beyer synthesis, leading to the 4-alkylquinoline, a synthesis using **6a** and 3,4-dimethylaniline was examined. This particular amine was chosen since the appropriate 6,7-disubstituted quinoline products would exhibit simple singlet first order NMR spectra for the carbocyclic ring protons which could be used quantitatively with the minimum possible chance of signal overlap. The main product obtained was **4h** (6% yield), supported by the low field singlet for H-2 at 8.37δ in the NMR spectrum which confirmed that both positions 3 and 4 were occupied. No **7c** could be detected in the initial product, a careful quantitative fractional crystallisation of the picrate derivative from ethanol was then performed. When, eventually, no more **4h** picrate separated, the remaining liquor (which was of low bulk) was evaporated to dryness. Decomposition of the residual picrate and analysis of the liberated bases by NMR then indicated the presence of some **7c**. The familiar A_3B_2 pattern for the Et group was readily apparent and in the low field region *two* H-2 signals were present, a singlet and a doublet, J = 4.3 Hz. The former was due to residual **4h** whilst the latter resulted from **7c** which was confirmed by the presence of an additional doublet for H-3 at 6.96δ ($J = 4.4$ Hz). From a comparison of the areas of the respective H-5 and H-8 signals the composition of the mixed product was assessed as 98.3 : 1.7 in favour of **4h**. The proportional of the 4-alkylquinoline formed in the Beyer synthesis is therefore very small and, as previously reported by Ardashev and Tertov[23] this may readily be removed by simple recrystallisation of the picrate derivative.

The major problem encountered in the earlier studies of the orientation effects in quinoline syntheses was the estimation of the composition of the mixed isomers obtained. Although the possibility of two isomeric products was originally noted in 1884 by Skraup,[26] very few of the early attempts to evaluate the ratio of isomers produced were successful or reliable. The fact that often the 7-substituted quinoline only was reported may be attributed to the frequently greater solubilities and lower m.ps of the 5-substituted quinolines and their salts, compared with those of the corresponding 7-isomer. It was not until 1962 that the composition of the products in the classical Skraup reaction with *m*-toluidine were eventually reliably clarified by Palmer[2] through the use of GLC and IR techniques. In addition the properties of **2a** (m.p. 37–38°, picrate m.p. 245–246°, see Tables 6 and 7) have frequently been quoted in error in the past, emphasising the many occasions when samples of **2a** were obtained and considered as pure,[1] but which were no doubt still contaminated with **1a**. In the present study it was therefore considered essential that the analytical methods used be unequivocal and hence three independent techniques were employed, (a) GLC; (b) ^{1}H NMR; (c) fractional crystallisation of the picrate derivative. The respective merits and deficiencies of these techniques will now be considered.

Palmer[2] has previously employed GLC for the analysis of isomeric quinoline mixtures, with a poly(propeneadipate) column. Fitzgerald[27] has concluded that the most useful phase for the separation of quinoline mixtures was diglycerol, however, the volatility limits of this material meant that good separations could only be effected at the cost of time and gradual loss of phase, however, this highly polar material did produce very symmetrical peaks. Rezl[28] has also reported satisfactory separations of methylquinolines on a diglycerol column. Diglycerol was therefore chosen for the present investigation. In all cases the 7-substituted isomer eluted before the corresponding 5-substituted isomer, but even with this column a complete separation of the two isomers could not be achieved. Although variation of instrument operating conditions did produce better separations, the increased tailing and broadening of the peaks made these alternatives unrealistic. Peak areas were estimated by comparison of the zones on either side of a perpendicular dropped from the base of the valley between the highly symmetric peaks. Although diglycerol afforded the best separation of the quinoline products, it did not prove possible to resolve the mixture of **3f** and **4f** by GLC, however, the alternative analytical procedures did indicate the presence of both components and a satisfactory estimation of the isomer ratio was obtained. With the diglycerol column 2-substituted compounds exhibited shortened retention times due to the "ortho effect" as noted by Fitzgerald.[27,29] The chromatographic data for the alkylquinolines are collected in Table 4.

^{1}H NMR spectroscopy proved to be the most valuable technique for the analyses of the isomeric quinoline products, the presence of a single or of multiple components was usually immediately evident. Mixtures of the 5- and 7-Me isomers featured two well resolved Me singlets, from which a satisfactory estimate of the isomer ratio was then obtained by comparison of peak areas from suitably expanded spectra. The identity of the products was assessed from the carbocyclic aromatic region, the **1** series isomers gave rise to a complex second order 3-spin multiplet whilst a readily analysed AMX spectrum was obtained for the **2** series isomers. For reactions commencing from 3,4-dimethylaniline the NMR spectra of the quinoline products were particularly simple. The carbocyclic ring protons of the **3** isomers appeared as two doublets, whilst those for the **4** isomers appeared as two broadened singlets. However, the alkyl signals from these isomers frequently overlapped, due to their greater abundance and similarity, accordingly the isomer ratios were obtained by comparison of appropriate aromatic signals. The NMR spectra of the quinoline products are shown in Table 5. Since the range of quinoline derivatives studied was quite extensive certain characteristic features of the spectra, which concern the *peri* positions 4 and 5 and which do not appear to have been rigorously established in the quinoline series, have been demonstrated. The H-4 proton generally absorbed at 7.6–7.8δ, introduction of a 5-methyl substituent resulted in a downfield shift to *ca* 8.0 δ. Similarly the H-5 proton which generally absorbed at 7.3–7.5δ, moved downfield to 7.5–7.7δ when a 4-Me substituent was present. The above shifts of *ca* 0.2 ppm are examples of *peri*-deshielding effects, which have been noted for other substituents in polycyclic systems,[30] and also in the methylcoumarin series.[31] The recognition of *peri*-deshielding effects is important for the assignment of certain signals, particularly that corresponding to the H-4 proton, which may occur either upfield or downfield from H-8 in alkylquinoline derivatives. Two examples are provided by **4f** (H-4: 7.52δ, H-8: 7.67δ—each broadened singlets) and **3b** (H-4: 7.96δ, H-8: 7.65δ—each doublets, *peri*-deshielding effect present). A *peri*-deshielding effect should also occur in the NMR spectrum of 5-ethylquinoline, accordingly our published partial spectrum[5] for this compound is incorrect, the signal at 8.14δ should be re-assigned to H-4, and the coupling constants re-designated as $J_{34} = 8.7$ Hz, $J_{24} = 1.8$ Hz, and $J_{48} = 0.8$ Hz.

The third technique used in the identification of reaction products was fractional crystallisation. This is an old established method[32] which is nevertheless capable of excellent results. Fractional crystallisation of the mixed picrate derivative from ethanol presented a convenient and reliable technique for the isolation of pure samples of the 7- or 6,7-substituted isomers which were present in the larger proportion and always separated first from ethanol. These crystallisations were performed only in order to secure an authentic sample of one pure isomer for identification purposes, no attempt was made to obtain the other isomer in a pure state. The results obtained are shown in Table 6. Comparison of the melting points of the initial and final samples of the picrates permits the presence of one or more compounds to be deduced as exemplified below. In the case of **4g** picrate the increase in m.p. was slight (1°) and represented recrystallisation only, accordingly only one isomer was present. The m.p. of **4a** picrate increased quite

Table 4. Gas–liquid chromatographic data for alkylquinoline derivatives (20% diglycerol column at 140°)

Substituted quinoline	Relative retention time (a)	Ratio 1 / 2 or 3 / 4
1a	1.43	1.17
2a	1.22	
1b	1.22	1.17
2b	1.04	
1c	1.75	1.14
2c	1.53	
1d	2.91 (b)	1.29 (b)
2d	2.25	
1f	0.95	1.11
2f	0.85	
2g	1.78	
2h	- (c)	
2j	- (c)	
3a	2.54	1.11
4a	2.28	
3b	2.06	1.11
4b	1.85	
3c	3.01	1.09
4c	2.75	
3d	5.35 (b)(d)	1.32 (b)
4d	4.05 (d)	
3f	1.65 (e)	
4f	1.65 (e)	
4g	3.19	
4h	- (c)	
4j	- (c)	

a - Relative to quinoline = 1.00.
b - Tentative result only.
c - Retention time too long, single peak only obtained with 10% silicone SE52 column at 225°.
d - Very broad peak.
e - 3f / 4f did not separate.

significantly from 260–262° to 278–279° which indicated that a separation had been achieved and that the original sample must therefore have been a mixture of **3a** and **4a**, as subsequently confirmed by GLC and NMR analyses. Similar increases in m.p. (in the range 8–18°) were obtained for all of the other **1**/**2** and **3**/**4** couples prepared, including **3f** and **4f** which were not separable by GLC (see Table 4). Certain results from the fractional crystallisation experiments were, however, of little value. The initial sample of **4c** picrate melted at 198–202°, whilst the final m.p. increased considerably to 245–246°. Since the von Miller-Kinkelin procedure is known to produce a mixture of four potential products in this case[29,33] it was not possible to deduce the proportion or even the existence of mixed 5,6- and 6,7-isomers. Hence the necessity for the use of GLC and NMR techniques. However, in the majority of cases, consideration of the m.ps of the picrate derivatives presents a reliable method by which the existence of one or two isomeric products may readily be established, without the need of other analytical equipment. Since the technique of fractional crystallisation is well established[32] it is perhaps surprising that more reliable results were not obtained by some of the earlier workers.

The results of the orientation effect studies are collected in Table 3 and the properties of the synthesised quinoline derivatives are shown in Tables 7 and 8. It is apparent that the ratios of **1**:**2** and of **3**:**4** are largely unaffected by the introduction of substituents at the 2- and/or 3-positions only, but that the introduction of a 4-Me group caused the proportion of the 5- or 5,6-substituted isomer to be reduced to almost zero. (A very small quantity of a product suspected to be **3d** was detected by GLC). In the presence of 2,4- and 3,4-dimethyl- and of 2,3,4-trimethyl-substituents, none of the **1** or **3** substituted isomers could be detected. This last result was also substantiated from the results of the orientation effects studies (1-condensation vs 3-condensation of methyl ketones **6**) in the Beyer synthesis with 3,4-dimethylaniline. The initial product obtained was mainly **4h** (98.3%); after careful fractional crystallisation of the picrate derivative, a residue remained which con-

Table 5. ^{1}H NMR spectra of alkylquinoline derivatives (a)

Compound	Chemical shift (δ) H-2	H-3	H-4	H-5	H-6	H-7	H-8	Methylene groups and coupling constants
1b	(2.64)	7.08	7.98	(2.55)	7.24 - 7.48 (b)		*ca.* 7.8 (b)	J_{34} 8.6 Hz
1f	(1.33)	(2.28)	7.79	(2.47)	(b)	(b)	7.80	CH_2 : 2.86 δ $J_{CH_2CH_3}$ 7.5 Hz
2b	(2.63)	7.04	7.80	7.50	7.15	(2.51)	7.69	J_{34} 8.3 Hz, J_{56} 8.3 Hz J_{68} 1.7 Hz
2c	8.56	(2.45)	7.67	7.47	7.18	(2.52)	7.73	J_{24} 2.1 Hz, J_{56} 8.4 Hz J_{68} 1.7 Hz
2d	8.55	6.94	(2.52)	7.66	7.18	(2.47)	7.78	J_{23} 4.2 Hz, J_{56} 8.4 Hz J_{68} 1.8 Hz
2f	(1.34)	(2.37)	7.59	7.42	7.12	(2.49)	7.70	CH_2 : 2.96 δ $J_{CH_2CH_3}$ 7.5 Hz J_{56} 8.3 Hz, J_{68} 1.7 Hz
2g	(2.53)	6.81	(2.46)	7.59	7.11	(2.46)	7.66	J_{56} 8.4 Hz, J_{68} 1.8 Hz
2h	8.43	(2.34)	(2.49)	7.68	7.16	(2.45)	7.69	J_{56} 8.5 Hz, J_{68} 1.7 Hz
2j	(2.56)	(2.26)	(2.44)	7.64	7.12	(2.48)	7.62	J_{56} 8.6 Hz, J_{68} 1.8 Hz
3b	(2.60)	7.02	7.96	(2.40)	(b)	7.27	7.65	J_{34} 8.5 Hz, J_{78} 8.5 Hz
3f	(1.34)	(b)	7.83	(2.46)	(b)	7.27	7.67	CH_2 : 2.86 δ $J_{CH_2CH_3}$ 7.5 Hz J_{78} 8.2 Hz
4a	8.64	7.13	7.83	7.38	(2.40, 2.43) (c)		7.74	J_{23} 4.2 Hz, J_{34} 8.3 Hz J_{24} 1.9 Hz
4b	(2.60)	7.00	7.70	7.30	(2.33, 2.38) (c)		7.67	J_{34} 8.2 Hz
4c	8.51	(2.39)	7.62	7.32	(2.44, 2.45) (c)		7.71	J_{24} 2.2 Hz
4d	8.48	6.93	(2.54)	7.50	(2.38)	(2.38)	7.71	J_{23} 4.3 Hz
4f	(1.34)	(2.37)	7.52	7.27	(2.37, 2.40) (c)		7.67	CH_2 : 2.85 δ $J_{CH_2CH_3}$ 7.5 Hz
4g	(2.55)	6.84	(2.51)	7.46	(2.39)	(2.39)	7.63	
4h	8.37	(2.33)	(2.44)	7.50	(2.38)	(2.38)	7.64	
4j	(2.54)	(2.25)	(2.43)	7.44	(2.37)	(2.37)	7.55	
7c	8.50	6.96	(1.34)	7.55	(2.38)	(2.38)	7.72	CH_2 : 2.97 δ $J_{CH_2CH_3}$ 7.5 Hz

a - 100 MHz, CCl_4, δ p.p.m. from T.M.S. Compounds 1b, 1f, 3b, 3f and 7c were studied in admixture with 2b, 2f, 4b, 4f and 4h respectively. Values in parentheses are for the appropriate substituted methyl group.

b - Peak(s) obscured by major isomer present in admixture.

c - Exact assignments uncertain.

Table 6. Melting points of quinoline picrate derivatives before and after fractional crystallisation

Quinoline Derivative	Initial picrate m.p.	Final picrate m.p. (a)	Lit. m.p.
2a	235° (c,f)	245-6° (e)	242° (3) 245° (2)
2b	180-2° (c)	194-5° (e)	196° (3)
2c	197-202° (c,g)	239-40° (e)	240.5° (7) 244° (3)
2d (b)	233-4°	235-6°	230° (8)
2f	211-3° (c)	222-3° (e)	219-20° (11)
2g	233-4°	235-6°	234-6° (9)
2h	227-8° (h)	228-9° (e)	229° (3)
2j	215-6°	217-8°	-
4a	260-2° (d)	278-9° (e)	278° (3)
4b	202-5° (d)	221-2° (e)	-
4c	198-202° (d,g)	245-6° (e)	-
4d (b)	264-5°	266-7°	-
4f	220-1° (d)	228-9° (e)	-
4g	238-9°	239-40°	-
4h	249-50° (h)	251-2° (e)	-
4j	225-6°	227-8°	-

a - See Table 8 for elemental analyses.

b - Similar results obtained for products from the Knorr and Skraup reactions.

c - Also contains 5-isomer (GLC after decomposition).

d - Also contains 5,6-isomer (GLC after decomposition).

e - Single pure isomer (GLC after decomposition).

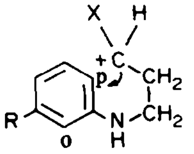
f - Manske *et al.*[3] give m.p. 235° for **2a** picrate before recrystallisation.

g - Also contains 2-ethyl substituted by-products.[29]

h - Also contains trace of 7c (see discussion).

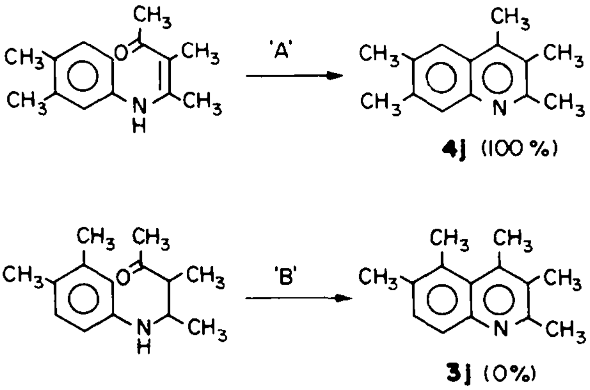
tained the second product **7c**. Since the minute proportion (1.7%) of the latter compound could readily be detected but the presence of any **3h** was still not apparent, then the extent of this alternative mode of cyclisation must be exceptionally low, and most probably zero. The lack of formation of the **1** or **3** isomers may be attributed to steric hindrance by the *peri*-substituted 4-Me group. Clearly ring closure by process "A" is much less subject to steric hindrance than by process "B" as illustrated in Scheme 1 for the case of **3j**/**4j**. It should be remarked that where a choice of cyclisation routes is possible, then the least hindered pathway occurred exclusively. However, in those cyclisation reactions leading to products in which *both* 4- and 5-Me groups were present, but where no alternative pathway was possible, then ring closure did still occur with little significant decrease in yield, as shown in Table 9.

The Skraup reaction has been considered[2] to be compatible with attack by a fully charged carbonium ion (e.g. **9**) on the position of maximum electron density.



9 X = NHAr or OH

With *m*-methyl- and 3,4-dimethyl-substituted aniline derivatives the enhanced proportion of the 7- or 6,7-isomer may be accounted for by several factors. Statistically, either isomer is equally possible, and electronically the weak inductive effect of the Me substituent(s) would not be expected to favour either route. It is therefore probable that the 7-isomer predominates



Scheme 1. Steric hindrance in quinoline syntheses.

mainly through steric effects since *para*-cyclisation is the least hindered pathway. That the *ortho*-cyclisation pathway is completely ineffective in the presence of an additional Me group leading to a 4-substituted quinoline clearly demonstrates the extreme sensitivity of the Skraup reaction to steric effects, and the exclusive selectivity of the least hindered pathway. It may therefore be concluded that unhindered *para*-cyclisation is always preferred, when possible, except when a *para* electron withdrawing group (such as *m*-nitro)^2 is present which can exert such a strong effect as to outweigh the steric hindrance.

Table 7. Properties of quinoline derivatives (a)

Compound	Yield (%) (b)	Initial m.p.	Lit. m.p.	Final m.p. (c,d)	Lit. m.p.
2a	71	b.p. 255-60°/760 mm. n_D^{20} 1.6147	b.p. 257.6°/760 mm. (34) $n_D^{20.8}$ 1.6149 (35)	m.p. 37-8°	39° (34)
2b	19	b.p. 264-6°/760 mm.	b.p. 265°/745 mm. (36)	m.p. 59-60°	61° (3)
2c	17	-	b.p. 270-1.5° (7)	m.p. 78-9°	80° (3)
2d	44 (e)	b.p. 280-5°/760 mm.	b.p. 283° (37)	b.p. 284°/757 mm.	b.p. 283° (37)
2d	52 (f)	b.p. 280-5°/760 mm.	-	b.p. 283-4°/760 mm.	-
2f	6	25-32°	40-1° (11)	40-1°	40-1° (11)
2g	85	b.p. 283-5°/760 mm.	-	b.p. 283-5°/760 mm. n_D^{22} 1.5990	b.p. 103-4°/1.5 mm. n_D^{20} 1.5997 (9)
2h	9	73-6°	-	76-7°	78° (3)
2j	17	114-6°	79° (10)	119-20°	-
4a	68	50-5°	-	57-8°	58° (3)
4b	16	60-70°	69-70° (12)	73-4°	-
4c	22	80-95°	-	111-2°	-
4d	37 (e)	90-5°	-	95-6°	-
4d	44 (f)	92-5°	-	95-6°	-
4f	20	95-103°	-	113-4°	-
4g	90	76-9° (b.p. 308-9°/772 mm.)	-	79-80°	79-80° (15)
4h	6	118-22°	-	124-5°	124-5° (16)
4j	22	144-6°	-	145-6°	144-5° (16)

a - For NMR spectral data see Table 5, for properties of picrate derivatives see Table 6.

b - Initial yield of (mixed) quinolines.

c - Purified product, from decomposed picrate derivative after fractional crystallisation.

d - For elemental analyses see Table 8.

e - Via Knorr synthesis (% yield from 2-chloro-4-methylquinoline given).

f - Via Skraup synthesis.

Table 8. Elemental analyses of quinoline products

	Molecular	Calc. (%)			Found (%)		
Compound	Formula	C	H	N	C	H	N
2f	$C_{13}H_{15}N$	84.3	8.2	7.6	84.4	7.9	7.7
2f picrate	$C_{19}H_{18}N_4O_7$	55.1	4.4	13.5	55.3	4.3	13.6
2j	$C_{13}H_{15}N$	84.3	8.2	7.6	84.2	8.2	7.5
2j picrate	$C_{19}H_{18}N_4O_7$	55.1	4.4	13.5	55.3	4.2	13.7
4b	$C_{12}H_{13}N$	84.2	7.7	8.2	84.5	7.8	8.3
4b picrate	$C_{18}H_{16}N_4O_7$	54.0	4.0	14.0	53.9	4.1	13.8
4c	$C_{12}H_{13}N$	84.2	7.7	8.2	84.6	7.9	8.3
4c picrate	$C_{18}H_{16}N_4O_7$	54.0	4.0	14.0	53.9	4.1	13.9
4d	$C_{12}H_{13}N$	84.2	7.7	8.2	84.4	7.7	7.9
4d picrate	$C_{18}H_{16}N_4O_7$	54.0	4.0	14.0	53.8	4.2	14.0
4f	$C_{14}H_{17}N$	84.4	8.6	7.0	84.3	8.4	6.9
4f picrate	$C_{20}H_{20}N_4O_7$	56.1	4.7	13.1	56.3	4.7	13.1
4g picrate	$C_{19}H_{18}N_4O_7$	55.1	4.4	13.5	55.0	4.4	13.6
4h picrate	$C_{19}H_{18}N_4O_7$	55.1	4.4	13.5	55.2	4.3	13.7
4j picrate	$C_{20}H_{20}N_4O_7$	56.1	4.7	13.1	55.9	4.6	12.8

Table 9. Synthesis of polymethylquinolines

Aniline reactant	Quinoline product	Yield (%)	Ref.
3,4-dimethyl-	2,4,5,6-tetramethyl- (3g)	0	a
3,4-dimethyl-	2,4,6,7-tetramethyl- (4g)	90	a
2,5-dimethyl-	2,4,5,8-tetramethyl-	90	22
2,4,5-trimethyl-	2,4,5,6,8-pentamethyl- (8)	90	a

a - This work.

It has also recently been shown in these laboratories[31] that similar orientation effects occur with the Pechmann reaction between an asymmetric methylphenol and malic acid which leads to a mixture of the 5- and 7-methylcoumarin, whilst with ethylacetoacetate the 4,7-dimethylcoumarin only is obtained.

The present study has been limited to steric effects by Me groups upon quinoline syntheses commencing with asymmetric methyl substituted anilines. Similar results have also been reported[5] for certain reactions starting with *m*-ethylaniline; the Skraup synthesis produced a mixture of 5- and 7-ethylquinoline, whilst the Combes reaction afforded 7-ethyl-2,4-dimethylquinoline only. Similar considerations would also be expected to apply to *m*-(higher alkyl) anilines, hence the reaction with *m*-(*n*-butyl) aniline would be expected to lead to a mixture of 5- and 7-*n*-butylquinoline rather than the 7-isomer only as previously indicated by Long and Schofield.[4] In order to obtain more substantiative conclusions further studies employing alternative substituents need to be performed. Roberts and Turner[38] have reported that the Combes reaction with *m*-chloroaniline leads to the exclusive formation of 7-chloro-2,4-dimethylquinoline **10**, which has also been confirmed in the present study. Accordingly, the suggestion of Campbell *et al.*[39] that the product of the reaction between *m*-chloroaniline and 1,3,3-trimethoxybutane was a mixture of 5-chloro-4-methylquinoline and 7-chloro-4-methylquinoline should therefore be viewed with caution. A re-investigation of this reaction is in progress and will be reported at a later date.

The direct synthesis of *peri*-substituted quinolines from *m*-alkyl- and *m*-halogeno-anilines *via* the hindered pathway is totally ineffective. Such a lack of formation of these derivatives could nevertheless prove to be of synthetic value. If a pure 7-substituted quinoline was required, and should in the particular application an additional 4-Me substituent be of no consequence, then introduction of such a group would result in the exclusive formation of the desired isomer and eliminate the need for a subsequent separation technique.

EXPERIMENTAL

M.ps were determined on a Kofler hot stage apparatus. ^{1}H NMR spectra were recorded at 100 MHz using Varian HA-100D and Jeol JNM-MH-100 instruments, chemical shifts are reported as ppm (δ) downfield from TMS. GLC analyses were performed on a Perkin-Elmer model 800 gas chromatograph fitted with a flame ionisation detector and operated isothermally at 140° with a 4' column of 20% diglycerol on celite (60/80 mesh) and a nitrogen carrier gas flow rate of 80 ml/min. *m*-Toluidine (b.p. 203–204°/760 mm) and 3,4-dimethylaniline (b.p. 226–227°/760 mm, m.p. 50–51°) were freshly redistilled before use.

Synthetic procedures

(i) *Heterocyclic ring unsubstituted* (the Skraup synthesis, preparation of **1a**/**2a** and of **3a**/**4a**). The general procedure of Clarke and Davies[40] was employed using the amine (0.2 mol), $FeSO_4$ (8 g), glycerol (68.7 ml, 0.94 mole), arsenic pentoxide (45.9 g, 0.2 mole) and conc H_2SO_4 (40 ml).

(ii) 2-*Substituted quinolines* (the Doebner–von Miller synthesis, preparation of **1b**/**2b** and of **3b**/**4b**). The general procedure of Mills *et al.*[41] was employed using the amine (0.2 mole), conc HCl (68 ml), freshly distilled acetaldehyde (22.0 g, 0.5 mole) and $ZnCl_2$ (5 g).

(iii) 3-*Substituted quinolines* (the von Miller–Kinkelin synthesis, preparation of **1c**/**2c** and of **3c**/**4c**). The general procedure of Claret and Osborne[29] was employed using the amine (0.33 mole), freshly redistilled propionaldehyde (30 ml), paraformaldehyde (10 g), $FeCl_3 \cdot 6H_2O$ (50 g), and fused $ZnCl_2$ (5 g) in ethanolic soln.

(iv) 4-*Substituted quinolines* (a) (the Skraup synthesis, preparation of **2d** and of **4d**). The general procedure of Campbell and Schaffner[42] was employed using the amine hydrochloride (0.0625 mole), $FeCl_3 \cdot 6H_2O$ (27 g), anhyd $ZnCl_2$ (1 g), EtOH (45 ml) and methyl vinyl ketone (95%, 4.2 ml, 0.05 mole).

4-*Substituted quinolines* (b) (the Knorr synthesis, preparation of **2d** and of **4d**). The general procedure of Ewins and King[8] was employed using the amine (0.22 mole) and ethylacetoacetate (30 g, 0.23 mole) to produce the aceto acetanilide derivative which was cyclised with conc H_2SO_4 (25 ml) to give the intermediate 4-methyl-2-quinolone. The appropriate 2-chloro-4-methylquinoline derivatives were synthesised by the general procedure of Michailov[43] using the quinolone (0.05 mole) and $POCl_3$ (9.3 g, 0.06 mole).

2-Chloro-4,7-dimethylquinoline (8.6 g, 90%) crystallised from EtOH as colourless needles, m.p. 49–50°. (Found: C, 68.9; H, 5.3; N, 7.4; Cl, 18.7. Calc for $C_{11}H_{10}NCl$: C, 68.9; H, 5.3; N, 7.3; Cl, 18.5%) NMR ($CDCl_3$): 2.51 (3H, s, Me–7), 2.57 (3H, s, Me–4), 7.01 (1H, s, H–3), 7.24 (1H, d of d, J_{56} 8.2 Hz, J_{68} 2.0 Hz, H–6), 7.64 (1H, bs, H–8), 7.68 (1H, d, J_{56} 8.2 Hz, H–5).

2-Chloro-4,6,7-trimethylquinoline (7.71 g., 75%) crystallised from EtOH as colourless needles, m.p. 137–138°. (Found: C, 70.2; H, 6.1; N, 6.9; Cl, 17.0. Calc for $C_{12}H_{12}NCl$: C, 70.0; H, 5.9; N, 6.8; Cl, 17.2%) NMR ($CDCl_3$): 2.42 (6H, s, Me–6 & 7), 2.56 (3H, s, Me–4), 6.99 (1H, s, H–3), 7.51 (1H, s, H–5), 7.62 (1H, s, H–8).

The 4-methylquinoline derivatives were obtained from the 2-chloro-4-methylquinolines by the general procedure of Michailov[43] using the chloroquinoline (0.03 mole), conc HCl (30 ml) and Sn dust (15 g).

(v) 2,3-*Disubstituted quinolines* (the Doebner–von Miller synthesis, preparation of **1f**/**2f** and of **3f**/**4f**). The general procedure of Mills *et al.*[41] was employed using the amine (0.2 mole), conc HCl (68 ml), freshly redistilled propionaldehyde (29.0 g, 0.5 mole) and $ZnCl_2$ (5 g).

(vi) 2,4-Disubstituted quinolines (the Combes synthesis, preparation of **2g**, **4g**, **8** and **10**). The general procedure of Bonner and Barnard[15] was employed using the amine (0.1 mole) and pentan-2,4-dione (11.0 g, 0.11 mole) to produce the intermediate crude anil which was then cyclised with conc H_2SO_4 (90 ml).

2,4,5,6,8-Pentamethylquinoline **8** (15.5 g, 80%) crystallised from hexane as colourless prisms, m.p. 72–73° (lit.[10] m.p. 75°) NMR (CCl_4): 2.33, 2.54, 2.57, 2.60, 2.74 (15H, 5s, Me), 6.83 (1H, s, H-3), 7.14 (1H, s, H–7). The picrate crystallised from EtOH as yellow needles, m.p. 183–184° (lit.[10] m.p. 171–172°).

7-Chloro-2,4-dimethylquinoline **10** (17.2 g, 90%) crystallised from light petroleum as colourless plates, m.p. 47–48° (lit.[38] m.p. 46.5–48.5°) NMR ($CDCl_3$): 2.64 (3H, s, Me–4), 2.68 (3H, s, Me–2), 7.03 (1H, s, H–3), 7.40 (1H, d of d, J_{56} 8.8 Hz, J_{68} 2.0 Hz, H–6), 7.81 (1H, d, J_{56} 8.8 Hz, H–5), 7.95 (1H, d, J_{68} 2.0 Hz, H–8).

(vii) 3,4-*Disubstituted quinolines* (the Beyer synthesis, preparation of **2h** and of **4h**/**7c**). The general procedure of Ardashev and Tertov[23] was employed using the amine (0.32 mole), butanone (0.56 mole), $FeCl_3 6H_2O$ (50 g), fused $ZnCl_2$ (5 g) and paraformaldehyde (9.2 g) in ethanolic HCl soln. The presence of **7c** was detected as described under "Analysis of reaction products" below and in the discussion.

(viii) 2,3,4-*Trisubstituted quinolines* (the Combes synthesis, preparation of **2j**, **4j** and 2,3,4-trimethylquinoline). The general procedure described in (vi) was employed using especially purified **5** (12.5 g, 0.11 mole).

Synthesis and purification of **5**. The method of Shepherd[21] afforded a product which was analysed by GLC and found to contain pentan-2,4-dione (5–10%) as an impurity. The crude **5** (32 g) was dissolved in MeOH (35 ml) and a hot filtered soln of copper acetate (90.8 g, 0.5 mole) in water (800 ml) added. The precipated Cu salt was dried and recrystallised several times from MeOH to give the complex as greyish-green plates, m.p. 197–204° (dec), (lit.[44] m.p. 200–230° (dec)). The purified salt was shaken with dil H_2SO_4 (600 ml), extracted with ether and dried ($MgSO_4$). Removal of the solvent left pure **5** (21% recovery) as a pale yellow liquid, b.p. 169–171°/759 mm (lit.[45] b.p. 170–172°/760 mm). The product was analysed by GLC and found to be free from pentan-2,4-dione. NMR (CCl_4): 1.20 (1.95 H, d, J 7 Hz, central Me keto), 1.79 (1.05 H, s, central Me enol), 2.07 (6H, s, terminal Me keto & enol), 3.52 (0.65 H, q, J 7 Hz, CH keto), 16.25 (0.35H, s, OH, enol).

2,3,4-trimethylquinoline (6.5 g, 38%) crystallised from hexane as colourless prisms, m.p. 94–95° (lit.[22] m.p. 92°) NMR (CCl_4): 2.25 (3H, s, Me–3), 2.44 (3H, s, Me–4), 2.56 (3H, s, Me–2), 7.28 (1H, m, H–6), 7.44 (1H, m, H–7), 7.73 (1H, m, H–5), 7.84 (1H, m, H–8), H–5 to H–8 formed an ABCD spin system. The picrate crystallised from EtOH as long yellow needles, m.p. 225–226° (lit.[22] m.p. 216°).

Analysis of reaction products

A sample of the initial product was analysed by GLC and NMR. The picrate derivative was prepared in EtOH soln,[5] collected, and washed with a little EtOH. The m.p. was then determined. The initial picrate was usually obtained as small or microscopic yellow needles. Decomposition with warm NaOHaq and analysis of the liberated bases by GLC usually indicated that no separation had been effected. However, in the case of the 2-substituted quinoline picrates, which were particularly soluble in EtOH, a partial separation was indicated. The initial picrate (1 g) was dissolved in boiling EtOH (200–2000 ml) and a fractional crystallisation performed to afford, after 2–3 days as the least soluble fraction, the pure (GLC, after decomposition) **2** or **4** picrate as slender long yellow needles. Decomposition of the pure **2** or **4** picrate with NaOHaq gave the appropriate quinoline base which, in the case of solid samples, was recrystallised from hexane. The properties of the quinoline bases and of their picrate derivatives are shown in Tables 6–8.

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REFERENCES

[1] L. Bradford, T. J. Elliott and F. M. Rowe, *J. Chem. Soc.* 437 (1947).
[2] M. H. Palmer, *Ibid.* 3645 (1962).
[3] R. H. F. Manske, L. Marion and F. Leger, *Can. J. Res.* **20B**, 133 (1942).
[4] R. Long and K. Schofield, *J. Chem. Soc.* 2350 (1953).
[5] P. A. Claret and A. G. Osborne, *Tetrahedron* **33**, 1765 (1977).
[6] O. Doebner and W. von Miller, *Ber. Dtsch Chem. Ges.* **16**, 2464 (1883).
[7] W. P. Utermohlen Jr., *J. Org. Chem.* **5**, 544 (1943).
[8] A. J. Ewins and H. King, *J. Chem. Soc.* **103**, 104 (1913).
[9] R. Adams and J. Campbell, *J. Am. Chem. Soc.* **72**, 1021 (1950).
[10] N. P. Buu-Hoi and D. Guettier, *Rec. Trav. chim.* **65**, 502 (1946).
[11] K. Harz, *Ber. Dtsch Chem. Ges.* **18**, 3384 (1885).

[12] L. Berend, *Ibid.* **17**, 653 (1884).

[13] W. Merz, *Ibid.* **17**, 1158 (1884).

[14] M. Gandino, *Belg. Pat.* 667,052 (1965).

[15] T. G. Bonner and M. Barnard, *J. Chem. Soc.* 4181 (1958).

[16] F. H. Case and H. H. Wisneski, *J. Heterocycl. Chem.* **5**, 789 (1968).

[17] *Beilsteins Handbuch der Organischen Chemie*, Vol. 20, p. 415. Springer-Verlag, Berlin (1935).

[18] O. Doebner and W. von Miller, *Ber. Dtsch Chem. Ges.* **17**, 1712 (1884).

[19] S. G. P. Plant and R. J. Rosser, *J. Chem. Soc.* 1861 (1929).

[20] L. Berend, *Ber. Dtsch Chem. Ges.* **17**, 1489 (1884).

[21] T. M. Shepherd, *Chem. & Ind.* 567 (1970).

[22] J. von Braun, W. Gmelin and A. Petzold, *Ber. Dtsch Chem. Ges.* **57B**, 382 (1924).

[23] B. I. Ardashev and B. A. Tertov, *Zh. Obshch. Khim.* **26**, 218 (1956); *J. Gen. Chem. U.S.S.R.* **26**, 233 (1956).

[24] A. T. Nielsen and W. J. Houlihan, *Org. Reactions* **16**, 31 (1968).

[25] M. T. Bogert and D. Davidson, *J. Am. Chem. Soc.* **54**, 334 (1932).

[26] Z. H. Skraup, *Monatsh. Chem.* **5**, 531 (1884).

[27] J. S. Fitzgerald, *Austral. J. Appl. Sci.* **12**, 51 (1961).

[28] V. Rezl, *Chem. prumysl.* **12**, 246 (1962).

[29] P. A. Claret and A. G. Osborne, *J. Chem. Tech. Biotechnol.* **29**, 175 (1979).

[30] L. M. Jackman and S. Sternhell, *Application of Nuclear Magnetic Resonance Spectroscopy in Organic Chemistry* pp. 204–207. Pergamon Press, Oxford (1969).

[31] A. G. Osborne, *Tetrahedron* **37**, 2021 (1981).

[32] See for example, L. Gatterman, *The Practical Methods of Organic Chemistry*. (Eng. Edn. transl. by W. B. Shober) pp. 11–14. Macmillan, New York (1896).

[33] W. von Miller and F. Kinkelin, *Ber. Dtsch Chem. Ges.* **20**, 1916 (1887).

[34] E. Jantzen, *Dechema Monograph.* No. **48**, 35 (1932).

[35] J. W. Brühl, *Z. Phys. Chem.* **21**, 385 (1896).

[36] A. M. Spivey and F. H. S. Curd, *J. Chem. Soc.* 2656 (1949).

[37] L. Knorr, *Annalen* **245**, 357 (1888).

[38] E. Roberts and E. E. Turner, *J. Chem. Soc.* 1832 (1927).

[39] K. N. Campbell, A. H. Sommers, J. F. Kerwin and B. K. Campbell, *J. Am. Chem. Soc.* **68**, 1851 (1946).

[40] H. T. Clarke and A. W. Davies, *Org. Synth.*, Coll. Vol. I, 478 (1948).

[41] W. H. Mills, J. E. G. Harris and H. Lambourne, *J. Chem. Soc.* **111**, 1294 (1921).

[42] K. N. Campbell and I. J. Schaffner, *J. Am. Chem. Soc.* **67**, 86 (1945).

[43] G. I. Michailov, *Zh. Obshch. Khim.* **6**, 511 (1936).

[44] D. P. Graddon and R. A. Schulz, *Austral. J. Chem.* **18**, 1731 (1965).

[45] A. W. Johnson, E. Markham and R. Price, *Org. Synth.* **42**, 75 (1962).