710. *The Skraup Reaction. Formation of 5- and 7-Substituted Quinolines.*

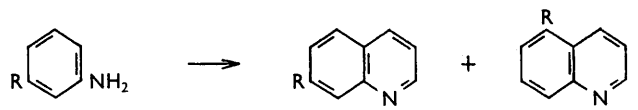
By M. H. PALMER.

The ratios of the isomeric quinolines formed in Skraup reactions of fourteen 3-substituted or 3,4-disubstituted anilines have been determined by physical methods.

In general, 3-substituted anilines lead to mixtures in which the 7-substituted quinolines predominate; however, exceptions occur where the substituent may deactivate the position *para* to it by electromeric shift (*e.g.*, *m*-nitroaniline gives mostly 5-nitroquinoline).

With 3,4-disubstituted anilines, examples are given where either the 5,6- or the 6,7-isomer is the major product; it is concluded that the electronic effects of the 4-substituent may control the course of the reaction where the 3-substituent is weakly *ortho-para* directing (*e.g.*, halogen).

ALTHOUGH the formation of 5- and 7-substituted quinolines during the Skraup reaction with *m*-substituted anilines is well known,[1] comparatively few attempts have been made either to obtain quantitative data concerning the ratio of isomers or to propound a general theory which will predict the major isomer. Bradford, Elliot, and Rowe,[2] who made a detailed study of nine reactions of this type, with *m*-nitrobenzenesulphonic acid as oxidising agent, concluded that strong *ortho-para* directing groups (*e.g.*, I; R = Me, OMe) lead to the 7-substituted quinoline (II) only, whereas more weakly *ortho-para* directing



(I) (II) (III)

groups (*e.g.*, I; R = Cl) gave predominantly the 7-isomer. *meta*-Directing groups (*e.g.*, I; R = NO_2) gave both isomers, the 5-isomer being predominant. However, the normally *meta*-directing trifluoromethyl group of *m*-trifluoromethylaniline [3-5] led predominantly to the 7-substituted quinoline. Furthermore, the Skraup reaction with *m*-dimethylaminoaniline gives [2] mainly the 7-isomer, although the dimethylamino-group is *meta*-directing in strong acid.

These reactions have been re-investigated with both 3-substituted and 3,4-disubstituted anilines. The ratios of isomers in the resulting quinolines were determined by gas chromatography, except for the mixtures of higher boiling point, which were analysed by infrared spectroscopy. The 7-substituted quinolines showed strong absorption near 825 and 875 cm.$^{-1}$ (two free hydrogen atoms and one free hydrogen atom respectively in the aromatic ring),[6] the 5-isomers near 800 cm.$^{-1}$ (three free hydrogen atoms), the 6,7-disubstituted quinolines near 880 and 890 cm.$^{-1}$ (one free hydrogen atom), and the 5,6-disubstituted quinolines near 830 cm.$^{-1}$ (two free hydrogen atoms) (see Table 1). The separated isomers, isolated by fractional crystallisation, were used as reference samples.

The results obtained (Tables 2—4) suggest that the ratio of 7- to 5-substituted quinoline is virtually the same whether the reaction conditions are similar to those described by Rowe and his co-workers [2] or to those normally used.[1] The failure of earlier workers [2] to isolate the second isomer in some cases may be ascribed to the frequently greater solubilities and

[1] Manske and Kulka, *Org. Reactions*, 1953, **7**, 66.
[2] Bradford, Elliott, and Rowe, *J.*, 1947, 437.
[3] Gilman and Blume, *J. Amer. Chem. Soc.*, 1943, **65**, 2467.
[4] Poutermann and Girardet, *Experientia*, 1947, **3**, 28.
[5] Belcher, Stacey, Sykes, and Tatlow, *J.*, 1954, 3846.
[6] Bellamy, " The Infra-red Spectra of Complex Molecules," 2nd Edn., Methuen, London, 1958.

TABLE 1.

Some frequencies in the infrared absorption spectra of 5- and 7-substituted quinolines.

Substituents	Band frequencies (cm.$^{-1}$)	Substituents	Band frequencies (cm.$^{-1}$)	
5-F	796vs	7-F	829vs	867m
5-Cl	795vs	7-Cl	828vs	868m
5-Br	794vs	7-Br	828vs	875m
5-I	793vs	7-I	828vs	880m
5-Me [a]	801vs	7-Me [a]	829vs	880m
5-CF_3	801vs	7-CF_3	836vs	880m
5-OMe	795vs	7-OMe	830vs	850m
5-OEt	795vs	7-OEt	829vs	852m
5-Cl, 6-Me	832vs	7-Cl, 6-Me	878vs	885m
5,6-Cl_2	826vs	6,7-Cl_2	876vs	885m
5,6-Me_2	828vs	6,7-Me_2	882vs	894m
5-NO_2	800vs	7-NO_2	770vs	841m
5-NMe_2	797vs	7-NMe_2	820vs	845m

[a] Shindo and Ikekawa, *Pharm. Bull. Japan*, 1956, **4**, 292, give: 5-Me, 801s; 7-Me, 884s, 828s, cm.$^{-1}$.

TABLE 2.

Yield and isomer ratio of 5- and 7-chloro- and -methyl-quinolines.

Amine (I) (moles)	Sulphuric acid Concn. (% w/w)	Vol. (ml.)	Initial reflux temp.	Yield [a] (%)	% Composition of mixture [b] 5- (III)	7- (II)
R = Cl (0·2)	90	147	168°	57 [c]	47·5	52·5
	80	165	152	84	48·0	52·0
	70	165	132	73·5	45·5	54·5
	60	165	128	38	41·5	58·5
	50	265	120	8	38·5	61·5
R = Me (0·2)	90	147	170	56 [d]	39·3 [e]	60·7
	80	165	155	92·5	40·7	59·3
	70	165	140	87·5	39·8	60·2
	60	180	125	35	35·4	64·6

[a] The general method of ref. 2 was used. [b] By gas chromatography. [c] B. p. 130—135°/15 mm. [d] B. p. 123—126°/15 mm. [e] Rowe and his co-workers [2] isolated 7-methylquinoline only. Skraup and Brunner (*Monatsh.*, 1886, **7**, 140) and Poutermann and Girardet [4] obtained mixtures in which the 7-isomer predominated, in the latter case being 80% of the total product.

lower melting points [7] of the 5-substituted quinolines and their salts; thus, the separation of 5,6-dichloroquinoline (major component) from the 6,7-isomer proved difficult.

(IV) (V) (VI) (VII)

The slightly higher proportion of the 5-isomer obtained in reactions with *m*-chloroaniline and *m*-toluidine when the acid strength was increased (cf. ref. 2) may be ascribed to greater randomisation of the reactions at higher temperatures. In none of the reactions studied was the reverse effect noted.

From reactions with the *m*-halogenoanilines under comparable conditions (ref. 2, with the use of 70% w/w sulphuric acid) it is clear that steric factors cannot be important in this series. The increase in the proportion of *ortho* to *para* cyclisation (leading to 5- and 7-substituted quinolines respectively) as the electronegativity of the halogen atom decreases, parallels, but is less marked than, nitration of the halogenobenzenes.[8] This suggests that the inductive ($-I$) effect is more important than the mesomeric ($+E$) effect

[7] Lempert and Robinson, *J.*, 1934, 1419.
[8] Ingold, "Structure and Mechanism in Organic Chemistry," Cornell University Press, Ithaca, New York, 1953.

TABLE 3.

Yield and isomer ratio of other 5- and 7-substituted quinolines.

Amine (I) (moles)	Sulphuric acid Concn. (% w/w)	Vol. (ml.)	Initial reflux temp.	Yield (%)	B. p.	Composition of mixture (%) 5- (III)	7- (II)
R = OMe (1·20)	70	825	138	29·7 [a]	139°/15 mm.	22 [b,d]	78
R = OEt (0·80)	70	500	122	21 [a]	157°/20 mm.	19 [b]	81
R = F (0·247)	70	200	142	73·5 [a]	233—236°	25 [b]	75
R = Br (0·186)	70	140	145	88 [a]	150—152°/15 mm.	46 [b,e]	54
R = I (0·10)	70	83	138	69 [a]	96—150°/0·2 mm.	49 [c,f]	51
R = CF_3 (0·20)	60	191	127	46·5 [a,g]	225—233°	42 [b,h]	58
R = NO_2 (0·20)	70	200	138	57 [a]	M. p. 55—61°	78 [c,]	22
R = NMe_2 (0·239)	70	420	143	24 [a]	165—225°/15 mm.	25 [c,k]	75
R = Cl (2·00)[l]	*ca.* 80	140	160	47	155—160°/25 mm.	34 [b,m]	66

[a] The general method of Bradford *et al.* [2] was used. All samples had acceptable micro-analyses. [b] By gas chromatography. [c] By infrared spectroscopy. [d] These figures may not represent the proportions of isomers initially formed, since differential hydrolysis of the ether linkages may have occurred, with the result that some of the quinoline was not isolated. Bradford *et al.* and Lempert and Robinson (*J.*, 1934, 1419), do not record the formation of the 5-isomer. [e] Isomer ratios, (II) : (III), previously recorded are 1 : 1 (ref. 2) and 3 : 1 (Tomita, Fujisawa, and Takao, *J. Pharm. Soc. Japan*, 1952, **72**, 905). [f] It has previously been considered (*e.g.*, Mirek, *Roczniki Chem.*, 1960, **34**, 1599) that iodoanilines are decomposed under the conditions of the Skraup reaction. 7-Iodoquinoline could not be induced to solidify; the compound, m. p. 103°, described by Claus and his co-workers (*J. prakt. Chem.*, 1893, **48**, 167, 170) is probably identical with 5-iodoquinoline now prepared from 5-aminoquinoline through the diazonium salt. [g] In another experiment, using the conditions of Gilman and Blume,[3] a mixture containing 60% of the 7-isomer was obtained in 52% yield. [h] Previously recorded isomer ratios, (II) : (III), are 2 : 1,[4] 3·38 : 1,[3] 3·54 : 1.[5] [i] Confirms earlier results (ref. 2; and Decker, *J. prakt. Chem.*, 1901, [2], **63**, 573). [j] Acetyl derivative used. [k] Both 5- and 7-dimethylaminoquinoline rapidly darkened. Bradford *et al.*[2] report a ratio (II) : (III) of 7 : 1. [l] Reaction with crotonaldehyde according to the conditions of Utermohlen (*J. Org. Chem.*, 1943, **8**, 544). [m] Confirms the result of Spivey and Curd (*J.*, 1949, 2658).

TABLE 4.

Yields and isomer ratios of 5,6- and 6,7-disubstituted quinolines.

Substituted aniline (moles)	Sulphuric acid Concn. (% w/w)	Vol. (ml.)	Initial reflux temp.	Yield (%)	B. p.	Composition of mixture (%) 5,6-	6,7-
3-Cl, 4-Me (2·00)	*ca.* 80	1400	170°	68 [c]	162°/15 mm.	46 [a,b,d]	54
3,4-Cl_2 (4·00)	*ca.* 80	3500	160	54 [c]	M. p. 65—69°	67 [a]	33
3,4-Cl_2 (0·05)	80	41		75 [c]	M. p. 65—80°	58 [a]	42
3,4-Me_2 (2·00)	*ca.* 80	1700	160	60 [c]	152—160°/15 mm.	30 [a,b,e]	70

[a] By gas chromatography. [b] By infrared spectroscopy. [c] Method according to the general conditions of Bradford *et al.*[2] [d] Marias and Bacheberg (*J.*, 1950, 2207) do not record an isomer ratio. [e] Manske, Marion, and Leger (*Canad. J. Res.*, 1942, **20***B*, 133) and Wibaut and Boer (*Rec. Trav. chim.*, 1955, **74**, 241) obtained mixtures in which 6,7-dimethylquinoline was the major isomer.

TABLE 5.

Ratio of isomers of quinolines from the amine (V).

R	NO_2 [a]	H [b]	H [b]	Me [b]	Cl [b]	OMe [c]	OEt [c]	OH [d]	NO_2 [e]	H [b]	Me [b]
R′	Cl	Cl	Br	Cl	Cl	Br	Br	Cl	Me	Me	Me
Ratio of (VII) to (VI)	65 : 37	52 : 48	54 : 46	54 : 46	40 : 60	mainly (VI)	mainly (VI)	only (VI)	50 : 50	60 : 40	70 : 30

[a] Lutz, Bailey, Martin, and Salsbury, *J. Amer. Chem. Soc.*, 1946, **68**, 1324. [b] Present paper. [c] Berkenheim and Antik, *J. Gen. Chem.* (*U.S.S.R.*), 1941, **11**, 537. [d] Ghosh, Bannerjee, and Lasker, *J. Indian Chem. Soc.*, 1944, **21**, 354; Gupta, *J. Indian Chem. Soc.*, 1952, **29**, 711. [e] Huisgen, *Annalen*, 1948, **559**, 101. Calculated from the amount of (VII) obtained after removal of (VI) by reaction.

(IV). In the present work there was no correlation between the yield and electronegativity of the halogen atom.[9]

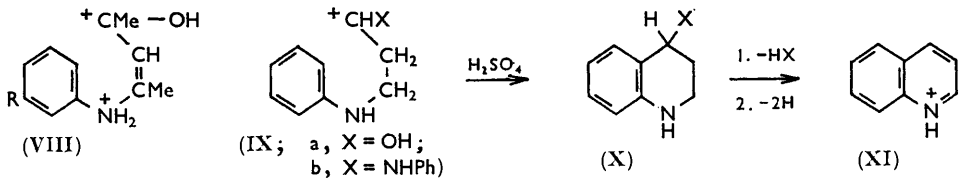
m-Halogenoaniline (I; R =)	F	Cl	Br	I
Ratio of quinolines (II) : (III)	3·0	1·2	1·17	0·96

[9] Mirek, *Roczniki Chem.*, 1960, **34**, 1599.

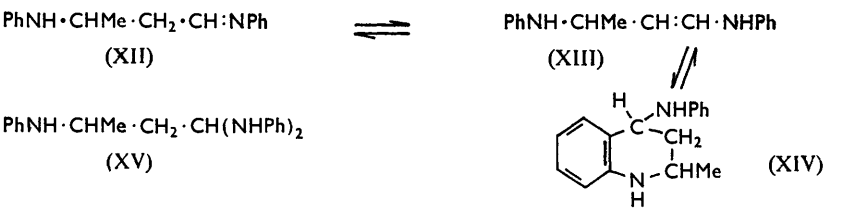
The formation of predominantly 5-substituted quinolines from Skraup reactions on anilines containing *m*-nitro-,[2] carboxylic acid,[2] or sulphonic acid [2] groups may be ascribed to *para*-deactivation by electromeric shift as postulated for the formation of 1,5-naphthyridine from 3-aminopyridine,[10] and 1'-phenylpyrazolo(4',5' : 2,3)pyridine from 4-amino-1-phenylpyrazole,[11] although in the latter case the poor yield probably reflects deactivation of both positions.

The formation of predominantly 5,6-dichloroquinoline in Skraup reactions with 3,4-dichloroaniline contrasts with those using 3,4-dimethylaniline and *m*-chloroaniline (Tables 2 and 4). These results, together with those reported in the literature (Table 5), indicate, in the case of weakly *ortho-para* directing groups (*e.g.*, halogen), a trend in favour of 5,6-disubstituted quinolines as the electron-donating power of the substituent *para* to the amino-group increases.

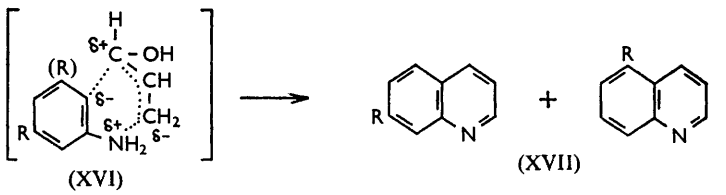
The Skraup reaction is generally considered to proceed with the intermediate formation of the β-arylaminocarboxaldehyde or a Schiff base derived from it,[12] then cyclisation to



a tetrahydroquinoline followed by elimination of water (or arylamine) and oxidation of the resulting dihydroquinoline. Cyclisation *via* a diprotonated species (VIII) has been claimed for the analogous Combes synthesis; [13] in contrast with that reaction,[14] however, the Skraup reaction may be used to prepare 6- and 8-alkoxyquinolines.[15] These



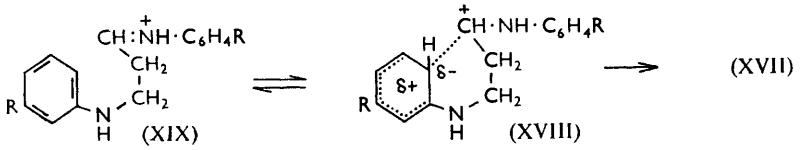
mechanistic differences can be interpreted as cyclisation through the anil (IXb) (or possibly a diprotonated species) in the latter case; the reported [16] ring–chain tautomerism of anils



of this type (XII—XIV) and the formation [17] of quinaldines by treatment of crotonylidineaniline with aromatic amines in acid solution supports this reaction scheme [the

[10] Hauser and Reynolds, *J. Org. Chem.*, 1950, **15**, 1224.
[11] Finar and Hurlock, *J.*, 1958, 3259.
[12] Manske, *Chem. Rev.*, 1942, **30**, 113.
[13] Bonner and Barnard, *J.*, 1958, 4176.
[14] Bradsher, *Chem. Rev.*, 1940, **28**, 463.
[15] Ardashev and Minkin, *Zhur. obshchei Khim.*, 1958, **28**, 545.
[16] Zalukaev and Razuvaev, *Bull. Acad. Sci. Latvian S.S.R.*, 1951, **1**, 131, **3**, 469 [see Ardashev, *J. Gen. Chem.* (*U.S.S.R.*), 1954, **24**, 127].
[17] Ardashev, ref. 15.

advantageous effect of an excess of aromatic amine is probably due to suppression of hydrolysis of the anil (XII) rather than cyclisation *via* the trianilinobutane (XV)].[17] The rates of reaction of *m*-substituted anilines relative to aniline itself, now determined from competitive experiments, contrast with relative rates of cyclisation[13] of substituted



4-anilinopent-3-en-2-ones (Combes reaction), indicating that the initial amino–acraldehyde reaction is not an electrophilic substitution, and thus a synchronous mechanism (XVI) is improbable.

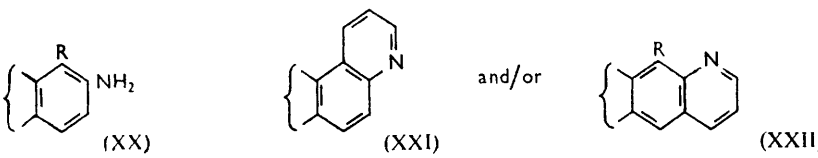
The observation that inductive effects are more important than conjugative electron

Relative rate experiments in the Skraup and Combes syntheses.

Reactant	Me	F	Cl	Br
Skraup (I) k_R/k_H	2·10	0·26	1·73	1·20
Combes[13] (VIII) k_R/k_H	*ca.* 700	5·12	2·24	1·88

release by the substituent in the Skraup reaction on *m*-substituted anilines is compatible with attack by a fully charged carbonium ion[18] (XVIII) on the position of maximum electron density [a similar mechanism would apply if cyclisation does occur *via* β-arylaminopropionaldehyde (IXa)].

A survey[1,19,20] of Skraup reactions where elimination of some substituents [*e.g.*, (XX); R = Cl, Br, NO_2, CO_2H, PhN_2, SO_3H but not Me, Et, $PhCH_2$, Ph] from the position of preferred cyclisation is observed, supports this mechanism, the substituent being eliminated as a cation. In the formation of 5,6-benzoquinoline from 1,2-diamino-



naphthalene,[19h] cyclisation is probably preceded by oxidation of the 1-amino-group. The difference in direction of ring closure observed in the Skraup reaction with 1,5- or 1,6- and 1,8-dihalogeno-2-naphthylamines[20c,d] (only the latter giving the angular isomer) may be ascribed to steric interaction between the *peri*-substituents facilitating halogen release. The Skraup cyclisations[20j] on 1-chloro- and 3-bromo-2-aminoanthraquinones (leading to linear and angular isomers respectively) parallel the lack of specificity shown by 2-aminoanthraquinone.[20b]

Experimental

M. p.s are corrected, b. p.s are uncorrected.

Reagents and Methods.—Aniline, *m*-chloro- and *m*-fluoroaniline, *m*-toluidine, *m*-anisidine, *m*-phenetidine, 3,4-dichloroaniline, 3-chloro-4-methylaniline, and 3,4-dimethylaniline were commercial materials; purification by fractional distillation was carried out where necessary

[18] Klyne and de la Mare, *Progr. Stereochem.*, 1958, **2**, 65.
[19] Huisgen, *Annalen*, 1948, **559**, 101.
[20] (*a*) Allen, *Chem. Rev.*, 1950, **47**, 275; (*b*) Bally and Scholl, *Ber.*, 1911, **44**, 1656; (*c*) Clemo and Driver, *J.*, 1945, 829; (*d*) Clemo and Legg, *J.*, 1947, 539; (*e*) Gerhardt and Hamilton, *J. Amer. Chem. Soc.*, 1944, **66**, 479; (*f*) Lellmann and Schmidt, *Ber.*, 1887, **20**, 3154; (*g*) Tortelli, *Gazzetta*, 1886, **16**, 366 (cf. ref. 2); (*h*) Yokote, Tanabe, and Shibata, *J. Chem. Soc. Japan, Ind. Chem. Sect.*, 1951, **54**, 476; (*i*) B.P., 427,485; (*j*) G.P., 565,968.

and each compound was shown to be pure by gas chromatography. The column (185 cm. × 0·4 cm.) was packed with nickel stearate (20% w/w) on Embacel, and was operated between 120° and 170° with nitrogen as carrier gas (20 ml./min.) at an inlet pressure of 10—15 lb./in.^{2}, and the outlet was at atmospheric pressure. A hydrogen-flame ionisation detector coupled with a Sunvic recorder gave a linear response. Under these conditions complete resolution of *ortho-*, *meta-*, and *para*-isomers occurred, except for the isomeric trifluoromethylanilines which were separated on a column (150 cm. × 0·4 cm.) packed with poly(propene adipate) (20% w/w) on Embacel and operated at 132°. In this case the carrier stream of nitrogen (20 ml./min.) was at an inlet pressure of 3·5 lb./in.^{2} and a katharometer detector was used.

Quinoline mixtures were analysed by using a column (185 cm. × 0·4 cm.) packed with poly(propene adipate) (5% w/w or 20% w/w) on Embacel at temperatures of 115—212°, with nitrogen as carrier gas (20 ml./min) at an inlet pressure of 7—15 lb./in.^{2}. A hydrogen-flame ionisation detector coupled to a Sunvic recorder gave a linear response. Peak areas, as calculated from (height × width at half the height), were shown to be accurate to approximately 2% by analysis of weighed mixtures. Contrary to earlier work [21] relative retention times for the substituted quinolines varied with the age of the column packing.

Infrared absorption spectra were determined in a double-beam spectrophotometer (Perkin–Elmer model 21) with carbon disulphide solutions for the quinoline mixtures, and liquid films or potassium bromide for the pure isomers.

m-Nitroaniline was converted into *m*-iodonitrobenzene, m. p. 31—33° (93%), and then into *m*-iodoaniline, b. p. 144—147°/15 mm. (74·5%), by Baeyer's method.[22] *NN*-Dimethylaniline was converted [23] into its *m*-nitro-derivative, m. p. 56—58° (43%), which, on hydrogenation at 70 lb./in.^{2} in ethanol with a 2% platinum oxide catalyst, gave *m*-amino-*NN*-dimethylaniline, b. p. 156°/20 mm. (100%).

Skraup Reactions.—Where possible these were carried out under the conditions given below for the reaction with *m*-chloroaniline. Variations in this procedure are then given.

Skraup Reaction with m-*Chloroaniline.*—A mixture of *m*-chloroaniline (25·5 g.), sodium *m*-nitrobenzenesulphonate (56·4 g.), glycerol (41·6 ml.), and sulphuric acid (concentration and amount as indicated in Table 2) was heated under reflux for 4 hr. (the initial reflux temperatures are shown in Table 2). Unchanged *m*-chloroaniline was decomposed by adding sodium nitrite (25% w/v; 55·0 ml.), heating to boiling, and steam distilling the mixture. The cooled reaction mixture was basified with 70% w/v sodium hydroxide, and steam distilled. Extraction of the distillate with chloroform (5 × 250 ml.) gave, after drying ($MgSO_4$) and removal of the solvent, a mixture of 5- and 7-chloroquinoline (b. p. 130—135°/15 mm.). (Yields and compositions of the mixtures are recorded in Table 2; all specimens had correct microanalyses.)

Skraup Reaction with m-*Iodoaniline.*—*m*-Iodoaniline (22·0 g.), glycerol (22 ml.), sodium *m*-nitrobenzenesulphonate (28 g.), and sulphuric acid (70% w/w, 83 ml.) were heated under reflux (initial temperature 138°) for 5 hr. Sodium nitrite (25% w/v; 28 ml.) was added and the mixture was boiled to decompose *m*-iodoaniline. After extraction with benzene (2 × 100 ml.) the mixture was basified at 0° with sodium hydroxide (70% w/v) and extracted with chloroform (4 × 200 ml.). Drying ($MgSO_4$) and removal of the solvent gave a mixture of 5- and 7-iodoquinoline, b. p. 96—150°/0·2 mm. (17·5 g., 69%) (Found: C, 42·4; H, 2·4; I, 49·7; N, 5·4. Calc. for C_9H_6IN: C, 42·3; H, 2·4; I, 49·8; N, 5·5%); it contained 51% of the 5-isomer [infrared spectroscopy, measurement on bands at 812 and 793 cm.$^{-1}$ (5-isomer) and 763, 774, 828, and 885 cm.$^{-1}$ (7-isomer)].

Skraup Reaction with m-*Trifluoromethylaniline.*—In one experiment the method was identical with that given for *m*-iodoaniline. In another experiment the conditions given by Gilman and Blume [3] were used.

Skraup Reaction with m-*Acetamidodimethylaniline.*—*m*-Acetamidodimethylaniline (42·5 g.) was added to a mixture of glycerol (60 ml.), sulphuric acid (70% w/w; 420 ml.), and sodium *m*-nitrobenzenesulphonate (72 g.) at 100°, and the mixture was heated to boiling for 6 hr. (initial reflux temperature 143°). The cold solution was added dropwise under the surface of concentrated ammonia (*d* 0·90; 3·5 l.) at −10°. The precipitate was boiled with ether, and the extracts combined with ethereal extracts (5 × 100 ml.) of the aqueous solution. Distillation

[21] (*a*) Fitzgerald, *Austral. J. Appl. Sci.*, 1961, **12**, 51; (*b*) Brown and Buck, *Chem. and Ind.*, 1961, 714.
[22] Baeyer, *Ber.*, 1905, **38**, 2759.
[23] Groll, *Ber.*, 1886, **19**, 200.

TABLE 6.

Physical constants of 5- and 7-substituted quinolines.

	B. p. or m. p.	n^{20}	Found C	Found H	Found N	Found Hal.	Calc. C	Calc. H	Calc. N	Calc. Hal.
5-F [a]	107—108°/15 mm.	1·5915	73·2	4·4	9·7	12·8	73·5	4·1	9·5	12·9
Picrate	199·5—200·5° (Me_2CO–EtOAc)									
5-Cl [b]	43°		—	—	8·1	21·6	—	—	8·6	21·6
Nitrate	160° (water)									
5-Br [c]	47—48°		51·2	2·9	6·7	—	51·9	2·9	6·7	—
Hydrogen oxalate	153—155° (EtOH)									
5-I [d]	104—105° (Et_2O)		42·3	2·4	5·0	49·8	42·3	2·4	5·5	49·8
5-OMe [e]	140°/15 mm.	1·6170	75·0	5·8	9·3	—	75·5	5·7	8·8	—
Hydrogen oxalate	156° (EtOH)									
5-OEt *	160°/15 mm.	1·6008	75·2	7·0	8·1	—	76·3	6·35	8·1	—
Hydrogen oxalate	153—154° (EtOH)									
5-Me [f]	129°/15 mm.	1·6121	84·1	6·3	9·8	—	83·9	6·3	9·8	—
Picrate	218—221° ($HCO{\cdot}NMe_2$)									
5-CF_3 [g]	215°	1·5379	61·1	3·1	6·7	—	60·9	3·05	7·1	—
Hydrogen oxalate	134—136° (EtOH)									
5-NO_2 [h]	70° (EtOH)		62·1	3·7	—	—	62·15	3·45	—	—
5-NMe_2 [i]	175°/15 mm.		50·5	3·6	17·6	—	50·9	3·7	17·5	—
Picrate	183—185° (EtOH)									
5-Cl, 2-Me [j]	142·5—143°/14 mm.	1·6198	67·8	4·6	7·5	19·7	67·6	4·5	7·9	20·0
Trihydrate	52—54°									
Hydrogen oxalate	143—146° (EtOH)									
5,6-Cl_2 [k]	85·5—86·5° (hexane)		54·6	2·7	7·3	—	54·5	2·5	7·05	—
5,6-Me_2 [l]	45°		84·5	7·4	8·7	—	84·05	7·05	8·9	—
Picrate	200°									
7-F [a]	112°/15 mm.	1·5909	73·5	4·1	9·2	—	73·5	4·1	9·5	—
Nitrate	137—141° (EtOH)									
7-Cl [b]	31—31·5°		—	—	8·6	21·5	—	—	8·6	21·6
Dichromate	177—178° (water)									
7-Br [c]	32°		51·9	3·0	6·6	—	51·9	2·9	6·7	—
Nitrate	197—198° (water)									
7-I [d]	176—179°/10 mm.		42·2	2·5	5·45	49·6	42·3	2·4	5·5	49·8
Nitrate	202—203° (decomp.) (water)									
7-OMe [e]	153°/15 mm.	1·6214	75·5	5·8	9·2	—	75·5	5·7	8·8	—
Nitrate	200—201° (water)									
7-OEt *	160°/15 mm.	1·6072	76·2	6·6	8·3	—	76·3	6·35	8·1	—
Nitrate	174—176° (water)									
7-Me [f]	35—38°		84·5	6·6	9·75	—	83·9	6·3	9·8	—
Picrate	245° ($HCO{\cdot}NHMe_2$)									
7-CF_3 [g]	66—67°		61·3	3·2	7·3	28·3	60·9	3·05	7·1	28·9
7-NO_2 [h]	129—130°		61·9	3·4	—	—	62·15	3·45	—	—
7-NMe_2 [i]	180°/15 mm.									
Perchlorate	237—238°		48·7	4·8	10·0	—	48·4	4·75	10·25	—
7-Cl, 2-Me [j]	76—78°		67·75	4·65	7·9	—	67·6	4·5	7·9	—
6,7-Cl_2 *	132—134°		54·1	2·7	7·1	—	54·5	2·5	7·05	—
6,7-Me_2 [l]	56·5—58°		83·6	7·1	8·8	—	84·05	7·05	8·9	—

* New compound.

[a] Roe and Hawkins (*J. Amer. Chem. Soc.*, 1949, **71**, 1785) give: 7-fluoroquinoline, b. p. 129°/30 mm., n_D^{25} 1·5845; 5-fluoroquinoline, b. p. 123°/30 mm., n_D^{25} 1·5916 (picrate, m. p. 199—200°). [b] Rowe *et al.*[2] give: 7-chloroquinoline, m. p. 30° (dichromate, m. p. 178°); 5-chloroquinoline, m. p. 43° (nitrate, m. p. 159—161°). [c] Tomita, Fujisawa, and Takao (*J. Pharm. Soc. Japan*, 1952, **72**, 905) give: 7-bromoquinoline, m. p. 31—32·5° (nitrate, m. p. 199—200°); 5-bromoquinoline, m. p. 47—48·5° (hydrogen oxalate, m. p. 150—157°). [d] (*i*) Claus and Massau (*J. prakt. Chem.*, 1893, **48**, 170) give: 7-iodoquinoline, m. p. 103°; (*ii*) Claus and Grau (*J. prakt. Chem.*, 1893, **48**, 167) give: 5-iodoquinoline, m. p. 100°. [e] Rowe *et al.*[2] give: 7-methoxyquinoline, b. p. 287°/758 mm.; 5-methoxyquinoline, b. p. 282°/758 mm. (hydrogen oxalate, m. p. 156°). [f] Jantzen (*Dechema Monograph.*, 1932, No. 48, p. 117) gives: 7-methylquinoline, m. p. 39°; 5-methylquinoline, b. p. 262·7°, n_D^{25} 1·62195. [g] Gilman and Blume [3] give: 7-trifluoromethylquinoline, m. p. 66—68°; 5-trifluoromethylquinoline, b. p. 214—215°/732 mm., n_D 1·528 (hydrogen oxalate, m. p. 120—126°). [h] Rowe *et al.*[2] give: 7-nitroquinoline, m. p. 136°; 5-nitroquinoline, m. p. 70° (nitrate, m. p. 195°). [i] Rowe *et al.*[2] give: 7-dimethylaminoquinoline, b. p. 326°/751 mm. (perchlorate, m. p. 240°); 5-dimethylaminoquinoline, b. p. 292°/741 mm. (picrate, m. p. 184°). [j] Spivey and Curd (*J.*, 1949, 2658) give: 7-chloroquinaldine, m. p. 77—78°; 5-chloroquinaldine, b. p. 276—278°/754 mm. (trihydrate, m. p. 52—53°). [k] Claus and Schedler (*J. prakt. Chem.*, 1894, **49**, 365) give: 5,6-dichloroquinoline, m. p. 85°. [l] Manske, Marion, and Leger (*Canad. J. Res.*, 1942, **20***B*, 133) give: 6,7-dimethylquinoline, m. p. 58°; 5,6-dimethylquinoline, m. p. 50° (picrate, m. p. 201°).

of the solvent gave a mixture of 5- and 7-dimethylaminoquinoline (10 g., 23·5%), b. p. 165—225°/15 mm. (lit.,[2] b. p. 290—326°), containing about 75% of the 7-isomer [by infrared spectroscopy, measurements on bands at 797 cm.$^{-1}$ (5-isomer) and 820 and 845 cm.$^{-1}$ (7-isomer)]. After 2 weeks, 40% of the mixture had polymerised (shown by infrared spectroscopy).

Preparation of 5- and 7-Chloroquinaldines.—A solution of *m*-nitrobenzenesulphonic acid in sulphuric acid was prepared from nitrobenzene (3·24 kg.) and oleum (20%; 10 l.) at 70° for 6 hr. A portion (440 ml.) of this solution, water (200 ml.), sulphuric acid (98%; 140 ml.), and *m*-chloroaniline (255 g.) were heated, and crotonaldehyde (246 ml.) was added to the boiling solution (internal temperature 160°). After a further 2 hr. at 160° the whole was worked up, as in the previous experiments, to yield a semi-solid mixture of 5- and 7-chloroquinaldine (153·5 g., 47%), b. p. 155—160°/25 mm. (Found: C, 66·8; H, 4·7; Cl, 19·4; N, 7·7. Calc. for $C_{10}H_8ClN$: C, 67·6; H, 4·5; Cl, 20·0; N, 7·9%), containing 66% of the 7-chloro-isomer (by gas chromatography).

Separation of Mixtures of Isomeric Quinolines.—Liquid mixtures were converted into a suitable salt, frequently the nitrate, and the pure salt of the predominant isomer was obtained by fractional crystallisation. The initial filtrates from these crystallisations were basified and converted into another salt, frequently the hydrogen oxalate, from which the second isomer was obtained pure by fractional crystallisation. Semi-solid mixtures were filtered and the solid material fractionally crystallised giving the higher-melting isomer. The oily fractions obtained were converted into a suitable salt and the second isomer obtained by fractional crystallisation of this salt. The crude picrate of 5-methylquinoline was obtained by fractional crystallisation with repeated removal of the less-soluble 7-isomer, and then purified by recrystallisation from dimethylformamide. Fractional crystallisation of the 5,6- and 6,7-dichloroquinoline mixture from n-hexane gave the latter isomer, and, after evaporation, crystallisation of the initial filtrate (from ethanol) gave the 5,6-isomer.

Physical constants of the separated isomers are given in Table 6.

Competitive Reactions.—A mixture of aniline (37·2 g., 0·4 mole), the *m*-substituted aniline ($X{\cdot}C_6H_4{\cdot}NH_2$) (0·4 mole), glycerol (14·7 g., 0·16 mole), sodium *m*-nitrobenzenesulphonate (36 g.), and sulphuric acid (70% w/w, 165 ml.) was boiled for 4 hr. Aqueous sodium nitrite (25% w/v, 56 g.) was added, and the solution was steam-distilled. The mixture was basified (70% w/v NaOH) and steam-distilled, and the distillate was extracted with chloroform (5 × 100 ml.). After drying (Na_2SO_4) and removal of the solvent, the residual oil was examined by gas chromatography. The molar ratio (R), total substituted quinoline : quinoline, and ratio of rate constants (k_X/k_H) obtained by the equation used by Ingold and Shaw[24] are given below.

X	Me	F	Cl	Br
R	1·939	0·297	1·633	1·181
k_X/k_H	2·10	0·26	1·73	1·20

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[24] Ingold and Shaw, *J.*, 1927, 2918.