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ALKYLATION OF NITROGEN HETEROCYCLES—I
STERIC AND ELECTRONIC EFFECTS IN REACTIONS OF CINNOLINE

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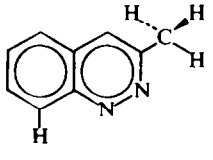
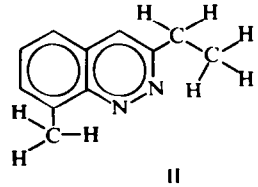
Abstract—A series of 3- and 3,4-alkyl substituted cinnolines have been prepared and their methylation by methyl iodide studied. An attempt has been made to separate reactivity at the N atoms into steric and electronic components, and it is shown that the greater reactivity of N-2 in this series results from steric effects. Alkylation product ratios in sterically balanced cinnolines show that the two N atoms have nearly identical properties. Some new observations on products formed in the Widman–Stoermer cinnoline synthesis are given.

ALTHOUGH various workers[1] have studied the alkylation of 3- and 4-hydroxy- or amino- substituted cinnolines, rather less is known about the alkylation (or indeed protonation) of cinnoline and its alkyl derivatives. Methylation of 4- and 3- methylcinnolines gives a 1- to 2- mixture in the ratio 10:90[2] and 40:60[3] respectively. These results show a higher degree of reactivity at N-2 and contrast with various π-electron density calculations which suggest a higher π-density at N-1;[4] at this point we note (a) that many attempts to correlate π-electron density with reactivity have been unsuccessful, (b) that the reactivity here is concerned with the σ-bonded system and that high π-density is not necessarily correlated with high σ-density, (c) that steric effects may well outweigh electronic effects, and that (d) in the special case of (reversible) protonation that (i) solvation of the ions could well be the critical factor in some instances (ii) total energy of the systems is more important than electron density. In the present work we study some aspects of b and c in the alkylation reactions (particularly methylation) of cinnolines which are generally considered to be irreversible under mild conditions; later we will describe parallel studies completed for indazole, and work on protonated systems where total energy is discussed. We have chosen to alkylate 3-alkyl substituted cinnolines, since in this case it is possible to nearly balance steric effects. Thus the peri 8-H in cinnoline is approximately sterically equivalent (I) to a 3-Me group; similarly an 8-Me group is nearly balanced (sterically)



I

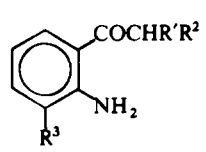


II

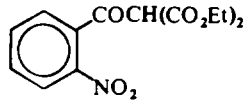
by a 3-tBu group (II), or an Et, i-Pr- or Ph-group in their least favourable conformations (see below). Since these alkyl groups are normally *o*-, *p*-activating to attack by electrophiles, it is necessary to balance their activating effect on N-2; this is approximately

done by introducing a similar group at C-4 since the *o*, *p*-electronic effects of these groups are similar.

Synthesis of cinnolines. A series of *o*-aminoacetophenones (III) were required for cyclization by the Widman–Stoermer reaction. The parent compound is best synthesized from *o*-nitrobenzoyl chloride with diethyl malonate (giving IV) followed by hydrolysis, decarboxylation and reduction with tin and acid.[5] A mixture of 3-toluic acid, fuming nitric acid and solid carbon dioxide at about −40° gave a mixture of 3-methyl-2-nitrobenzoic acid (V; 70%) and only 30% of the 5-Me isomer, in contrast to reactions at higher temperatures where the latter appears to predominate.[6] Conversion to the acetophenone was accomplished as above. Attempts to methylate the adduct (IV) with sodium ethoxide and methyl iodide failed,

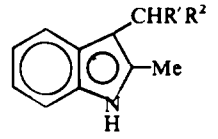


III

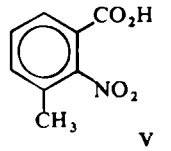


IV

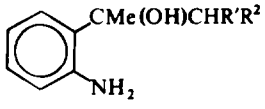
a: $R^1 = R^2 = R^3 = H$
b: $R^1 = Me, R^2 = R^3 = H$
c: $R^1 = R^2 = Me, R^3 = H$
d: $R^1 = Ph, R^2 = R^3 = H$



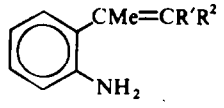
VI



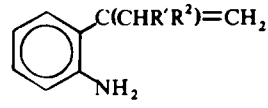
V



VII

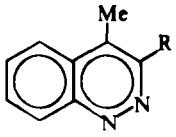


VIII

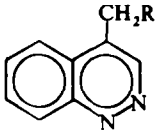


IX

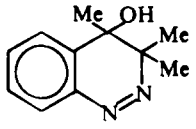
and the higher ketones (IIIb, c, d) were thus prepared from the indoles (VI) by periodate cleavage[7] and hydrolysis of the N-acetyl compound.[8] The synthesis of the tertiary alcohols (VII) was simple, but certain features of the NMR spectra of these compounds are described below. Dehydration of VII gave both olefins (VIII and IX) when phosphoric oxide in benzene is used. Furthermore the ratio of VIII to IX varied when either (i) the benzene solution or (ii) the benzene insoluble complex was worked up with aqueous ammonia; thus for VII (R^1 = Me, R^2 = H) the ratios of VIII to IX were: benzene solution 52:48 (25%) and phosphate complex 81:19 (75%) respectively. We have not explored the obvious synthetic utility of this partial separation. Cyclisation of the olefin mixtures (Table 2) in 7M HCl gave mixtures of the cinnolines (X + XI)[9] in the same proportions as the olefin precursors, thus showing that no interconversion of isomeric olefins takes place. This is consistent with our earlier observations[10] that deuterium exchange in olefins of these types fails even in strong deutero sulphuric acid. This may well be due to deactivation arising from preferential protonation of the amino groups. The mixed cinnolines (X + XI, a–d) were separated by chromatography on alumina, but only the 3,4-disubstituted compounds (Xa − Xd) and the benzyl compound (XId) could be induced to crystallise. The identity of the compounds XI a–c was established from their NMR spectra which



X



XI



XII

were effectively identical to 4-methylcinnoline but with differing 4-substituents; since they were not required further in this study they were not investigated further.

Apparently no tetrasubstituted olefins of type VIIIc have been cyclized in the Widman–Stoermer reaction. The solid product that we obtained from VIIIc was identified by NMR spectroscopy and mass spectrometry as XII or possibly an isomer of this. It had aromatic multiplets at τ 2·10 (1 proton, 8-H) τ 2·4–2·6 (3-protons, 5,6,7-H), singlets at τ 7·18 (1 proton, exchangeable with D_2O), 8·57, 8·68, 8·76 (each 3 protons). In its mass spectrum it showed abundant ions at *m/e* 190 (M^+), 148 ($(M—C_3H_6)^+$ presumed), 130 (further loss of water). Although the compound shows UV absorption at longer wavelength (458 nm) than expected by comparison with *trans*-phenylazobenzene (395 nm, no data being available for the *cis* isomer), the three non-equivalent Me groups, and downfield singlet (proton peri to lone pair electrons) eliminates most alternatives except 3-hydroxy-3,4,4-trimethyl-3,4-dihydrocinnoline. Since this compound is not critical to the present investigation further investigations will be reported elsewhere.

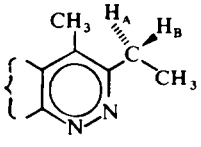
The remaining cinnolines studied, 3-phenyl- and 3-phenyl-8-methyl, were prepared by the Stolle–Becker synthesis from benzaldehyde phenyl- and *o*-tolyl-hydrazones by cyclization of the oxalyl chloride adduct with aluminium chlorides preferably in dichloromethane at low temperatures. Base catalyzed rearrangement of the intermediate isatins gave the cinnoline-4-carboxylic acids.

Alkylation of cinnolines. After boiling the cinnoline (10% w/v) with excess methanolic methyl iodide, the evaporated mixture was investigated by ^1H NMR spectroscopy. The relative intensities of the N-Me signals gave the product ratio (Table 3), the assignment of isomers being made by deuterium exchange of the alkyl substituents (at positions 1 to 4). Thus the α-benzylic protons of the 3-substituent in the 2-quaternary salt, and those of the 4-substituent in the 1-quaternary salt exchange readily in deuterium oxide at 35° containing traces of sodium carbonate. Under these conditions no exchange occurred with the other alkyl group at the 4- and 3-positions respectively. Although it was not used as a basis for assignment, deuterium exchange occurred much more rapidly in the 1- than the 2-Me groups. This is unlikely to be a steric effect since the environments were deliberately nearly balanced, but may be an indication that the ring is more electron attracting on a 1- than a 2-substituent. In these ratio determinations we estimate the error at $\pm 3\%$.

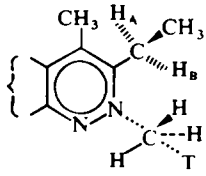
DISCUSSION

Although the conclusion that N-2 is more reactive than N-1 to protonation, methylation and N-oxidation,[12] has been disputed recently,[11] the results obtained from the reactions of 3,4-dimethyl-, and 3-methyl, 4-ethyl-cinnolines show that when the steric factors are balanced, that the reactivities of N-1 and N-2 are equal to within experimental error. As expected the larger groups, 3-ethyl-, isopropyl-, and

phenyl- in 4-methylcinnolines all give a higher proportion of 1-methylation than the above. The large difference between the 3-Et and 3-i-Pr group reactions is readily interpreted in terms of the conformations and differences between the 3-substituent and the 2- or 4-Me group in the transition state; thus as the Me group of CH_3-I approaches N-2 and a partial bond is formed, the Me group undergoes an S_N2 inversion, and appears larger than in the final state owing to the near planar nature of the intermediate. The 3-substituent thus "sees" nearly equal steric environments at each side. An Et group whose most probable conformation, i.e. one of highest population and longest lifetime is normally XIII, on reaction will be able to rotate to a conformation where the β-Me group is out of plane (XIV).



XIII



XIV

In the reacting state the conformation of the isopropyl compound will approximate to XIV but with H_B replaced by CH_3, and thus lead to considerably greater steric hindrance at N-2. The experiments show that the combined electronic and steric effects of a 3-Ph group are similar to those of a 3-Et group. The dihedral angle in biphenyl varies from 0° (crystalline state), through 20 ~ 25° (in solution) to 40 ~ 45°

TABLE 1. PHYSICAL PROPERTIES AND ^{1}H NMR SPECTRA OF THE *o*-AMINO KETONES (III) ^{1}H NMR SPECTRA-[a]

R_1	R_2	R_3	m.p. (b.p.)	3-H	4-H	5-H	6-H	NH_2	CHR_1R_2
H	H	H	20°[b]	3·45	2·80	3·50	2·38	3·50	7·53 (CH_3)
CH_3	H	H	45–6°[c]	3·40	2·78	3·50	2·31	3·80	*f*
CH_3	CH_3	H	(141–2°/20 mm)	3·40	2·77	3·48	2·27	3·80	7·5 (CH), 8·8 (CH_3)
Ph	H	H	105°[d]	3·40	*g*	3·50	*g*	4·00	*g*
H	H	CH_3	54–55°[e]	7·8 (CH_3)	2·80	3·42	2·38	3·60	7·52 (CH_3)

[a] In $CDCl_3$ (5–10% w/v).
[b] N. J. Leonard and S. N. Boyd (*J. Org. Chem.* **11**, 405 (1946)) gave m.p. 20°.
[c] B. L. Zenity and W. H. Hartung (*J. Org. Chem.* **11**, 444 (1946)) gave m.p. 47°.
[d] H. J. Schiefell and D. F. Detar (*Org. Syn.* **32**, 8 (1952)) gave m.p. 105–6°.
[e] J. R. Keneford, J. S. Morley and J. C. E. Simpson (*J. Chem. Soc.* 1702 (1948)) gave m.p. 56°.
[f] τ (CH_2) 7·5 τ (CH_3) 8·8, J = 7 Hz.
[g] Ph degenerate with H-4 and H-6.

(in the gas phase) and thus is clearly effected by intermolecular repulsions as well as internal 2,2'-, 6,6'-interactions and electronic effects.[13, 14] In the 4-substituted-3-phenylcinnoline series the twist (dihedral) angle is expected to be larger than in biphenyl under comparable conditions; thus it is possible that the steric hindrance

TABLE 2. OLEFIN MIXTURES[a] OBTAINED BY PHOSPHORIC OXIDE DEHYDRATION

R^1, R^2	R^1 = H, R^2 = Me	R^1 = H, R^2 = iPr	R^1 = R^2 = Me	R^1 = H, R^2 = Ph
IX	24	33	21	41
VIII	76	66	79	59

[a] Analysed by ^{1}H NMR spectroscopic integration of the olefin to aliphatic resonances.

to N-2 could *decrease* as the size of the 4-substituent increases. We note that while 4-methyl-3-phenylcinnoline gave 45% of the 2-methylated compound, none was found in the 4-unsubstituted case (the electronic effect of the 4-Me group will clearly activate N-1 preferentially). In two reactions where an 8-Me substituent was present

TABLE 3. PHYSICAL PROPERTIES AND NMR SPECTRA OF CINNOLINES

Substituents				^{1}H NMR spectra[a]					
3	4	8	m.p.	3	4	5	6	7	8
Me	Me	H	119–120°[b]	7·11	7·46	2·0	to	2·40[c]	1·60
Et	Me	H	51–52°[d]	6·76[e], 8·60[f]	7·45	2·0	to	2·48[c]	1·62
i-Pr	Me	H	98–99°[g]	6·40[e], 8·57[f]	7·42	2·0	to	2·40[c]	1·54
Me	Et	H	77–78°[b]	7·10	7·12[e], 8·75[f]	2·0	to	2·40[c]	1·60
Me	Et	NO_2	102–103°[b]	7·00	6·85[e], 8·70[f]	1·97	to	1·70	—
Et	Me	Me	74–75°[h]	6·73[e], 8·55[f]	7·40	2·13	to	2·53[c]	7·1
H	CH_2Ph	H	102–103°	0·95	5·72[i], 2·87[j]	2·0	to	2·60[c]	1·52
Ph	H	H	118–121°	1·8[l] 2·40 to 2·70[m]	2·0	2·1	to	2·40[c]	1·53
Ph	H	Me	57–58°	1·8[l] 2·40 to 2·60[m]	2·10	2·4	to	2·60[c]	7·03
Ph	CO_2H	H[k]	222–224°	1·75 to 2·1[j]	—	1·3[n]		1·75 to 2·1[c]	
Ph	CO_2H	Me[q]	240–242° (d)	2·62[l] 2·2[jm]	—	1·9	to	2·4[c]	6·9
Ph	Me	H[r]	126–127°[c]	2·20 to 2·60	7·30	2·0	to	2·40	1·45

[a] In $CDCl_3$.
[b] See Ref 12.
[c] Very degenerate ABC part of an ABCX spectrum.
[d] Found: C, 76·67; H, 7·01; N, 16·11: $C_{11}H_{12}N_2$ requires: C, 76·74; H, 6·97; N, 16·2%.
[e] Two protons, 1,3,3,1-quartet, J = 7 Hz.
[f] Three protons, 1,2,1-triplet, J = 7 Hz.
[g] Found: C, 77·25; H, 7·53; N, 15·05: $C_{12}H_{14}N_2$ requires: C, 77·41; H, 7·52; N, 15·05%.
[h] Found: C, 77·41; H, 7·52; N, 15·05: $C_{12}H_{14}N_2$ requires: C, 77·41; H, 7·52; N, 15·05%.
[i] Singlet, two protons.
[j] Protons superimposed on other aromatic protons.
[k] In dimethyl sulphoxide.
[l] AA′ part of AA′XX′Y spectrum superimposed on other aromatic protons.
[m] XX′Y part of AA′XX′Y spectrum superimposed on other aromatic protons.
[n] In an alternative assignment this could be the 8-H.
[p] Very degenerate set, superimposed on other aromatic protons.
[q] In trifluoroacetic acid.
[r] Found: C, 81·70; H, 5·42; N, 12·69: $C_{15}H_{12}N_2$ requires: C, 81·81; H, 5·45; N, 12·72%.

TABLE 4. METHIODIDES FORMED FROM THE CINNOLINES

	4-Me	3, 4-Me_2	3-Et, 4-Me	3-iPr, 4-Me	3-Ph, 4-Me	4-Et, 3-Me	4-Et, 3-Me, 8-NO_2
1-Methiodide	10	50	57	95	55	50	0
2-Methiodide	90[a]	50	43	5	45	50	100

	3-Ph	3-Ph, 8-Me	3-Et, 4, 8-Me_2
1-Methiodide	84	0	0
2-Methiodide	16[b]	100[b]	100

[a] Lund (Ref 2) also gives a 1:2 ratio of 10:90.

[b] Ames, Lund *et al.*, Ref 1. give a similar ratio but no experimental details of the isomer ratio determination.

TABLE 5. ^1H NMR SPECTRA OF CINNOLINE METHIODIDES

	Substituents			N_1–Me	N_2–Me	^1H NMR Spectra				
	3	4	8			3	4	5	6	7	8
(a)	Me	Me	H[b]	5·07	—	6·85	6·96	1·35	to		1·95
(b)	Me	Me	H[b]	—	4·95	6·85	6·96	1·35	to		1·95
(c)	Et	Me	H[b,c]	4·92	—	6·48, 8·45	6·87	1·40	to		1·90
(d)	Et	Me	H[b,f]	—	5·00	6·40, 8·43	6·92	1·35	to		1·85
(e)	i-Pr	Me	H[b,g]	4·90	—	6·10, 8·40	6·80	1·30	to		1·90
(f)	Me	Et	H[c]	5·05	—	6·46, 8·52	6·92	1·20	to		1·80
(g)	Me	Et	H[c]	—	4·93	6·49, 8·54	6·80	1·20	to		1·90
(h)	Me	Et	NO_2[d,h]	—	4·90	6·45, 8·50	6·65	0·90	1·32	0·90	—
(i)	Me	Et	Me[d,i]	—	5·10	7·03	6·53, 8·64	1·63	to	1·95	7·20
(j)	Ph	H	H[b]	4·80	—	0·6	1·7, 2·2–2·4	1·40	to		1·80
(k)	Ph	H	H[b]	—	5·20	0·6	1·7, 2·2–2·4	1·40	to		1·80
(l)	Ph	H	Me[b,j]	—	5·32		0·62	1·6	to	1·73	7·10
(m)	Ph	Me	H[a]	4·85	—	*k*	6·84	*k*	*k*	*k*	*k*
(n)	Ph	Me	H[a]	—	5·35	*k*	7·25	*k*	*k*	*k*	*k*

[a] Various solvents were used owing to solubility difficulties.

[b] In CF_3CO_2H.

[c] In D_2O.

[d] In $(CD_3)_2SO$.

[e] m.p. 212–213°; Found: C, 45·4; H, 4·4; N, 8·5; $C_{12}H_{15}N_2I$ requires: C, 45·85; H, 4·77; N, 8·92%.

[f] m.p. 159–160°; Found: C, 45·5; H, 4·6; N, 8·6; $C_{12}H_{15}N_2I$ requires: C, 45·85; H, 4·77; N, 8·92%.

[g] m.p. 174–175°; Found: C, 47·23; H, 5·02; N, 8·56%; $C_{13}H_{17}N_2I$ requires: C, 47·55; H, 5·18; N, 8·54%.

[h] m.p. 169–170°; Found: C, 55·3; H, 5·1; N, 15·9; $C_{12}H_{14}N_3O_2I$ requires: C, 55·6; H, 5·4; N, 16·2%.

[i] m.p. 173–174°; Found: C, 47·1; H, 4·7; N, 8·1; $C_{13}H_{17}N_2I$ requires: C, 47·55; H, 5·18; N, 8·54%.

[j] m.p. 173–174°; Found: C, 52·7; H, 3·7; N, 7·4; $C_{16}H_{15}N_2I$ requires: C, 53·0; H, 4·15; N, 7·74%.

[k] Complex multiplets from 1·2 to 2·4.

methylation gave solely the 2-quaternary salt; clearly only a 3-tertiary Bu substituent might have offset this steric effect, and we were prevented by synthetic difficulties from preparing such a system. It is significant that the reaction of these 3,4,8-trisubstituted cinnolines were very slow.

The above results clearly demonstrate the importance of steric effects in alkylation reactions of this type. These conclusions are supported by the all valency electron–molecular orbital calculations (CNDO and INDO methods) of the following paper.[15] The methylations of quinazoline and its 4-Me derivative to give the 3- and 1-quaternary salts respectively[16, 17] could well arise from steric control in the former, while the latter perhaps is more indicative of electronic reactivity. A further complication in much of the previous work in this field is the use of crystallization techniques and isolation weights to obtain the ratio of pure isomers in the mixtures.

NMR *spectra of the cinnolines.* The spectra of the cinnolines were generally complex overlapping multiplets at 60 and 100 mc/s. Even at 220 mc/s the spectra of 3-ethyl-4-methylcinnoline was not separate multiplets [in $(CD_3)_2SO$]; owing to the poor resolution obtained a complete analysis was impossible, but the ABXY spectrum gave the following approximate chemical shifts (τ): 8-H, 1·65; 5-H, 1·85; 6-H, 7-H, 2·20 with the aliphatic resonances as in Table 3. In trifluoroacetic acid this became more degenerate, with complex multiplets (two protons each) centred on 1·5 and 1·7, the 3-Et group at 6·50 (CH_2) and 8·35 (CH_3) and the 4-Me group at 6·90. Under these conditions we expect both 1-H and 2-H protonated species to be present in considerable concentration (*cf* Part II). The 1-methyl quaternary salt of this compound at 220 mc/s in trifluoroacetic acid was insufficiently resolved to show fine structure but it showed doublets at 1·45 and 1·55 (presumably H-8 and H-5) triplets at 1·66 and 1·82 whose intensities suggest the assignment 6-H and 7-H respectively; the aliphatic resonances were at 4·95 (N-CH_3), 6·62 (3-CH_2), 6·90 (4-CH_3) and 8·45 (3-CH_3). From this data it appears that further study at 220 mc/s, or higher, might lead to full analyses for all these complex ABCD type spectra.

EXPERIMENTAL

Ketones used in cinnoline synthesis. Two main methods of synthesis were used, depending upon whether or not the *o*-aminoacetophenone had a 2-substituent. The properties of the products are shown in Table 1.

Method A

3-Methyl-2-nitrobenzoic acid. m-Toluic acid (200 g) was added to fuming HNO_3 (600 ml) at −40° (sustained by the direct addition of solid CO_2). After 0·5 hr the solid was filtered and recrystallised to give the product (103 g) m.p. 222–223°. Dilution of the reaction medium gave after recrystallisation (H_2O) the 5-Me compound (54 g, m.p. 133–134°).

To dissolving Mg (18 g) in EtOH (17 ml) and CCl_4 (1·5 ml), ether (250 ml) and ethanolic (70 ml) diethyl malonate (117 g) was added. When homogeneous 3-methyl-2-nitrobenzoyl chloride (130 g) was added and the mixture boiled for 0·5 hr, acidification and extraction gave the diethyl 3-methyl-2-nitrobenzoyl malonate (100%). Hydrolysis and decarboxylation with conc H_2SO_4 (25 ml) in AcOH (200 ml) and water (120 ml) gave 3′-methyl-2′-nitroacetophenone (70 g, 63%) m.p. 85–6° (from light petroleum b.p. 100–120°). Reduction with Sn and HCl gave the aminoketone.

Method B

o-Amino-isobutyrophenone. Sodium metaperiodate (200 g) in water (600 ml) was added to 2-methyl-3-isopropylindole (88 g) in MeOH (600 ml). Filtration and extraction gave *o*-acetylamino-isobutyrophenone, which was boiled with HCl (34% w/v, 250 ml), water (250 ml) and EtOH (250 ml). Evaporation, neutralisa-

tion and extraction gave the ketone (48 g, 60%) b.p. 141–2°/20 mm. (Found: C, 73·0; H, 7·9; N, 8·5: $C_{10}H_{13}NO$ requires: C, 73·6; H, 8·0; N, 8·6%).

o-Aminophenylalkenes. The alcohols, prepared from the ketones by the action of the appropriate alkyl halide and Mg in ether, were heated with P_2O_5 in benzene for 3 hr. Hydrolysis with aqueous ammonia (d = 0·880) gave the olefin mixture (nearly 100%) which was analysed by ^{1}H NMR spectroscopy. The results are shown in Table 2.

Widman–Stoermer reactions

Typical reaction, synthesis of 4-methyl-3-phenylcinnoline and 4-benzylcinnoline. The olefin mixture (IX:VIII = 40:60%) in HCl (12 M, 50 ml) and water (10 ml) was treated with $NaNO_2$ (2·4 g) in water (10 ml) at −10°, and then after 0·5 hr heated to 60° for 5 min. Non-basic material was extracted with ether, the aqueous layer basified and extracted with ether, dried and evaporated. Analysis by ^{1}H NMR spectroscopy showed the mixture to contain 4-methyl-3-phenylcinnoline (60%) and 4-benzylcinnoline (40%): these were readily separated by chromatography on alumina and had the properties shown in Table 3.

Stollé–Becker syntheses

8-Methyl-3-phenylcinnoline-4-carboxylic acid. N-Benzylideneamino-N-(*o*-tolyl)oxamate was prepared (15 g), from benzaldehyde-*o*-tolylhydrazone (22 g) and oxalyl chloride (29 g). Cyclization was accomplished by $AlCl_3$ (50 g) in CH_2Cl_2 (300 ml) at −10° giving benzylideneamino-7-methylisation (70%), m.p. 162–3°, singlets τ 0·58 and 7·45, eight aromatic protons τ 2·20 to 3·10 (in $CDCl_3$). This compound (15 g) in NaOH aq (20% w/v, 360 g) was boiled for 1 hr, acidified and the product m.p. 240–2° dec separated; it had a singlet at τ 6·9 (CH_3), degenerate multiplets at τ 2·0 (5-H, 2′-H, 6′-H) and τ 2·2 (6-H, 7-H, 3′-H, 4′-H, 5′-H). Decarboxylation in benzophenone (20% w/w) under N_2 at 200° and extraction with ether from acid soln gave after basification 8-methyl 3-phenylcinnoline m.p. 57–8° (from light petroleum b.p. 40–60°).

Methylation of cinnolines. The following procedure was used, the only variable being reaction time, and this was estimated from the ^{1}H NMR spectrum of the mixture at various intervals in preliminary experiments, such that no starting material was observed.

4-Methyl-3-phenylcinnoline 1- and 2-methiodides. The cinnoline (0·6 g, 0·003 mole) in MeOH (15 ml) and MeI (4·2 g, 0·030 mole) was boiled for 5 hr. Vacuum evaporation gave the mixed quaternary salts whose ^{1}H NMR spectrum showed the mixture to contain 38% 2-methiodide and 62% 1-methiodide. Separation of the mixture was accomplished by fractional precipitation from EtOH by ether; the 1-methiodide had m.p. 213–5° (dec) and the 2-methiodide m.p. 179–181° (dec).

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