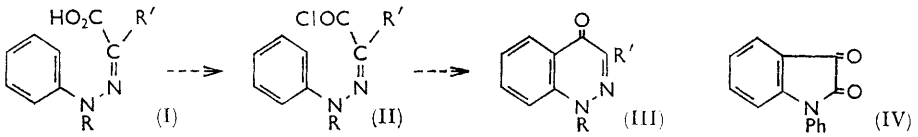
258. *A New Cinnoline Synthesis. Part II.*[1] *Synthesis of 1-Substituted 4-Cinnolone-3-carboxylic Acids.*

By H. J. Barber and E. Lunt.

Cyclisation of α-carbethoxyglyoxylyl chloride *N*-substituted phenylhydrazones (II; R′ = CO_2Et) under Friedel–Crafts conditions analogous to those used with the corresponding unsubstituted derivatives gave 1-substituted 4-cinnolone-3-carboxylic acids. With a 1-phenyl substituent, the acid was decarboxylated under vigorous conditions to the 1-phenyl-4-cinnolone, but decarboxylation could not be achieved with the 1-alkyl derivatives. The spectra of these acids, however, showed marked similarity to those of known 1-alkyl-4-cinnolones.

After the successful synthesis in these laboratories of 4-hydroxycinnoline-3-carboxylic acids from mesoxalyl chloride phenylhydrazones [1] we attempted to extend this procedure to the synthesis of *N*-alkyl- or *N*-aryl-4-cinnolone-3-carboxylic acids from the corresponding *N*-substituted phenylhydrazones.

The *N*-substitution precluded diazotisation and thus the application of the diazo-coupling reaction for the preparation of the intermediate diester and diacid phenylhydrazones. After several unsuccessful attempts to condense *N*-alkyl-*N*-nitrosoanilines with diethyl malonate, the required diesters were finally obtained by condensation of diethyl mesoxalate with the appropriate α-substituted phenylhydrazines. Complete hydrolysis of these diesters gave the diacids (I; R′ = CO_2H) only in very low yields, and these diacids, prepared in this way or by reaction of the appropriate hydrazine with dibromomalonic acid, proved to be extremely unstable and unsuitable for the preparation



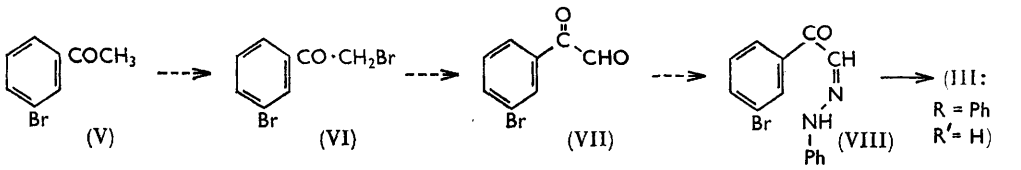
of diacid chlorides. The corresponding relatively stable half-esters (I; R′ = CO_2Et), however, were obtained in satisfactory yield by partial hydrolysis with one equivalent of alkali, and readily gave *N*-substituted half-ester acid chlorides (II; R′ = CO_2Et). These when cyclised *in situ* with titanium tetrachloride in nitrobenzene at 100° as previously described gave the *N*-substituted 4-cinnolone-3-carboxylic acids (III; R = Me, Et, or Ph, R′ = CO_2H) in moderate to good yields.

Decarboxylation of these carboxylic acids with *N*-alkyl substituents should, of course, give rise to 1-alkyl-4-cinnolones identical with those supposedly prepared by alkylation of 4-hydroxycinnolines under alkaline conditions [2,3] or by mild alkaline hydrolysis of 4-aminocinnoline quaternary salts.[3,4] Recently, however, Ames and Kucharska [5] have shown that these alkylation products are almost certainly 2-substituted derivatives, and have themselves isolated the authentic 1-alkylcinnolones as by-products in some cases. In practice, the acid (III; R = Me, R′ = CO_2H) could not be satisfactorily decarboxylated even under the most vigorous conditions. The infrared and ultraviolet spectra of these acids (III; R = Me or Et, R′ = CO_2H), however, showed marked similarity to those of a variety of *N*-alkyl-4-cinnolones (both 1- and 2-alkyl) prepared by the methods of Simpson and his co-workers [2,3] and of Ames and Kucharska.[5]

[1] Part I, Barber, Washbourn, Wragg, and Lunt, *J.*, 1961, 2828.
[2] Schofield and Simpson, *J.*, 1945, 512.
[3] Simpson, *J.*, 1947, 1653.
[4] Atkinson and Taylor, *J.*, 1955, 4236.
[5] Ames and Kucharska, *J.*, 1963, 4924; 1964, 283.

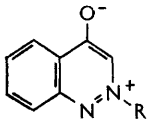
In order to obtain 1-alkylcinnolones by direct cyclisation for comparison with those obtained by the methods of Simpson [2,3] an attempt was made to extend the synthesis to cyclisation of *N*-substituted glyoxylyl chloride phenylhydrazones (II; R′ = H). The intermediate acids were prepared directly from the phenylhydrazines and dichloroacetic or dibromomalonic acid under mild alkaline conditions, and the acid chlorides were obtained as previously described. As was the case with the *N*-unsubstituted derivative [1] attempts to cyclise the acid chloride under the usual conditions gave no trace of any cinnoline.

In the case of the *N*-phenyl acid (III; R = Ph, R′CO_2H) decarboxylation was achieved by heating with copper chromite in refluxing quinoline giving the hitherto unknown 1-phenyl-4-cinnolone * (III; R = Ph, R′ = H) in low yield, in addition to *N*-phenylisatin (IV) presumably resulting from an oxidative ring contraction. Here, again, no direct comparison with authentic 1-phenyl-4-cinnolone was possible, although an attempt was made to prepare a sample by the alternative route shown below, ending with a benzyne-type ring closure analogous to that described for *N*-phenyltetrahydroquinolines by Huisgen and Konig.[8] The intermediates (V—VIII) were readily obtained by successive bromin-

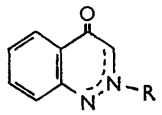


ation of acetophenone, first in the presence of aluminium chloride,[9] then in acetic acid [10] to give *m*-bromophenacyl bromide, which with dimethyl sulphoxide [11] gave *m*-bromophenylglyoxal. Attempted cyclisation of *m*-bromophenylglyoxal phenylhydrazone with sodamide in refluxing benzene led only to 80% recovery of the starting material, and pressure of other work precluded further investigation.†

The infrared and ultraviolet spectra of our decarboxylation product, however, showed marked similarity to that of the authentic 1-methyl-4-cinnolone described by Ames and Kucharska.[5] A marked feature of all the infrared spectra was the strong band in the region 1560—1600 cm.$^{-1}$, corresponding to the 4-carbonyl group, typical of all 4-cinnolones which we have examined.[13] With the acids the band at 1735—1745 cm.$^{-1}$ due to



(X)



(XI)

the carboxyl group was also clearly visible. The strong 4-carbonyl absorption was, unexpectedly, shown also by the 2-methyl substituted derivative (X), prepared by Ames and Kucharska [5] and by the corresponding 2-methyl- and 2-benzyl-6-chloro-derivatives.

* The compound m. p. 188°, believed by Bhat and Bose,[6] on evidence of method of synthesis and infrared spectral data, to be 1-phenyl-4-cinnolone, shows no *strong* carbonyl absorption in the 1560—1600 cm.$^{-1}$ region, typical of all 4-cinnolone derivatives we have studied and is thought unlikely to have this structure. Further work on the nature of this compound has been reported elsewhere.[7]

† Since this work was completed, further work on this type of benzyne reaction by Bunnett *et al.*[12] has shown this cyclisation to be unlikely on theoretical grounds.

[6] Bhat and Bose, *Chem. and Ind.*, 1963, 1930.
[7] Lunt and Threlfall, *Chem. and Ind.*, 1964, 1805.
[8] König and Huisgen, *Chem. Ber.*, 1959, **92**, 429.
[9] Pearson, Pope, Hargrove, and Stamper, *J. Org. Chem.*, 1958, **23**, 1412.
[10] Langley, *Org. Syn.*, Coll. Vol. I, p. 127.
[11] Kornblum, Powers, Anderson, Jones, Larson, Levand, and Weaver, *J. Amer. Chem. Soc.*, 1957, **79**, 6562.
[12] Bunnett, Kato, Flynn, and Skorcz, *J. Org. Chem.*, 1963, **28**, 1.
[13] Threlfall, private communication.

The possibility of at least a partial contribution in these compounds of 1,3-dipolar structures of the type (XI), similar to those postulated for the sydnones by Tien and Hunsberger [14] and Stewart and Danieli [15] has already been suggested.[7]

Experimental

(Except where stated, light petroleum refers to the fraction, b. p. 40—60°).

N-Substituted Phenylhydrazines.—*N*-Methyl-*N*-phenylhydrazine was prepared (64%) by zinc–acetic acid reduction of *N*-methyl-*N*-nitrosoaniline as described by Hartman and Roll [16] and had b. p. 49—52°/0·2 mm. The p-*nitrobenzaldehyde methylphenylhydrazone* (from ethanol) had m. p. 133—134° (Found: C, 65·9; H, 5·3; N, 16·6. $C_{14}H_{13}N_3O_2$ requires C, 65·9; H, 5·1; N, 16·5%). Similarly prepared were: *N*-Ethyl-*N*-phenylhydrazine (47%), b. p. 118—127°/16—17 mm. [p-*Nitrobenzylidene derivative* (from ethanol), m. p. 129—130° (Found: C, 67·6; H, 5·9; N, 15·7. $C_{15}H_{15}N_3O_2$ requires C, 67·0; H, 5·6; N, 15·6%)], and *NN*-diphenylhydrazine (79%), b. p. 116—122°/0·3 mm. [p-*nitrobenzylidene derivative* (from ethanol), m. p. 127—129° (Found: C, 71·9; H, 4·6; N, 13·3. $C_{19}H_{15}N_3O_2$ requires C, 71·9; H, 4·7; N, 13·3%)].

Diethyl mesoxalate N-*methylphenylhydrazone.* (*a*) *N*-Methyl-*N*-phenylhydrazine (12·2 g.) and diethyl mesoxalate [17] (17·4 g.) were refluxed in dry toluene (100 ml.) in a Dean and Stark separator in the presence of glacial acetic acid catalyst (0·1 ml.). When no more water was evolved (1·6 ml. collected in 4 hr.; theory 1·8 ml.) the toluene was removed under reduced pressure and the residue was distilled to give the crude ester (17·7 g.; 64%), b. p. 180—185°/0·1 mm., which later solidified. Crystallisation from light petroleum below 0° gave the pure *diester* (7·4 g.; 27%), m. p. 43—44° (Found: C, 60·7; H, 6·6; N, 9·9. $C_{14}H_{18}N_2O_4$ requires C, 60·4; H, 6·5; N, 10·0%).

(*b*) Alternatively, ethyl mesoxalate (34·8 g.) and *N*-methyl-*N*-phenylhydrazine (24·4 g.) in glacial acetic acid (50 ml.) were heated at 95° for 2 hr. The mixture was cooled and poured into water (1 l.), the solution was neutralised with sodium hydrogen carbonate, and the oil was extracted with ether (2 × 300 ml.). The dried (Na_2SO_4) extract afforded the crude ester (33·4 g.; 65%), b. p. 160—170°/0·01 mm., which was suitable for use in the hydrolysis stage. Similarly prepared were: diethyl mesoxalate *N*-ethyl-*N*-phenylhydrazone, b. p. 148—150°/0·05 mm. which did not crystallise and was hydrolysed to the half-ester (see below); and *diethyl mesoxalate* NN-*diphenylhydrazone*, m. p. 52—53° (Found: C, 67·5; H, 5·9; N, 8·2. $C_{19}H_{20}N_2O_4$ requires C, 67·1; H, 5·9; N, 8·25%).

Ethyl hydrogen mesoxalate N-*methyl*-N-*phenylhydrazone.* Diethyl mesoxalate methylphenylhydrazone (29·35 g.) in ethanol (150 ml.) was stirred at room temperature while 2·07N-ethanolic sodium hydroxide (51·2 ml.) was added in 5 ml. portions during 2 hr. Stirring was continued for a further 2 hr. when the mixture became neutral (phenolphthalein). After being poured into ice–water (1 l.), the mixture was filtered from unchanged diester (5·65 g.) the filtrate and washings were acidified (Congo Red) with hydrochloric acid, the separated orange oil was extracted with ether (2 × 350 ml.), and the extracts were washed with water and dried (Na_2SO_4). Evaporation of the ether gave the crude half-ester (20·1 g.) which solidified (m. p. 67—80°) when kept *in vacuo*. Crystallisation from ethyl acetate (100 ml.)–light petroleum (300 ml.) gave a product (11·9 g., 45%), m. p. 83—84°, sufficiently pure for further use. Further crystallisation from ethyl acetate–light petroleum gave the pure *half-ester*, m. p. 90—91° (Found: C, 57·3; H, 5·8; N, 11·5. $C_{12}H_{14}N_2O_4$ requires C, 57·6; H, 5·6; N, 11·2%).

The corresponding NN-*diphenylhydrazone* (63%), m. p. 133—134° (decomp.), was similarly obtained. Crystallisation from ethyl acetate–light petroleum gave the analytical sample, m. p. 134° (decomp.) (Found: C, 65·3; H, 5·25; N, 9·3. $C_{17}H_{16}N_2O_4$ requires C, 65·4; H, 5·1; N, 9·0%).

The ethyl hydrogen mesoxalate ethylphenylhydrazone, an orange syrup (94%) was obtained similarly and could not be solidified. It was cyclised directly to the cinnolone *via* the acid chloride prepared *in situ* as described below.

Mesoxalic acid methylphenylhydrazone. (*a*) *By hydrolysis.* Diethyl mesoxalate methylphenylhydrazone (16·9 g.) in refluxing ethanol (30 ml.) was treated with ethanolic sodium

[14] Tien and Hunsberger, *J. Amer. Chem. Soc.*, 1961, **83**, 178.
[15] Stewart and Danieli, *Chem. and Ind.*, 1963, 1926.
[16] Hartman and Roll, *Org. Syn.*, Coll. Vol. II, p. 418.
[17] Dox, *Org. Syn.*, Coll. Vol. I, p. 266.

hydroxide (2·4N; 25·5 ml.; 1 mol.). After the mixture had been refluxed for 2 min. a gelatinous sodium salt began to separate; the mixture was cooled, diluted with an equal volume of water, and treated with 2N-sodium hydroxide (61 ml.). After being heated at 60° for 15 min., the solution was cooled to 0° and acidified with hydrochloric acid. The gummy precipitate was separated by decantation, and triturated with ether–ethanol (4 : 1) to give the disodium salt (2·3 g.) of mesoxalic acid methylphenylhydrazone. The ethanol–ether filtrate afforded *ethyl glyoxylate methylphenylhydrazone*, b. p. 114°/0·05 mm., which crystallised from light petroleum below 0°, m. p. 46—47° (Found: C, 64·2; H, 6·9; N, 13·6. $C_{11}H_{12}N_2O_2$ requires C, 64·3; H, 6·8; N, 13·6%). The disodium salt when ground with 2N-hydrochloric acid (25 ml.) gave the free *diacid* as a yellow solid (1·7 g., 12%), m. p. 110° (decomp.) (Found: C, 54·7; H, 4·8; N, 12·8. $C_{10}H_{10}N_2O_4$ requires C, 54·2; H, 4·5; N, 12·6%). Attempted crystallisation from ethyl acetate–light petroleum led to lowering of melting point due to decarboxylation.

(*b*) *From dibromomalonic acid.* Dibromomalonic acid [18] (13·1 g.) was dissolved in water (50 ml.) and just neutralised with solid potassium carbonate. Further potassium carbonate (7 g.) was added, followed by a solution of methylphenylhydrazine (6·1 g.) in ethanol (50 ml.). The mixture was refluxed for 2 hr., and then kept overnight. Most of the ethanol was removed under reduced pressure and some oil which had separated was removed with ether (2 × 50 ml.). The aqueous layer, cooled in ice–salt, and carefully acidified with hydrochloric acid, gave a cream solid (6·5 g.), m. p. 133—134° (decomp.), consisting of a mixture of glyoxylic acid methylphenylhydrazone and the dipotassium salt of the required diacid. The glyoxylic derivative was removed by extraction with boiling benzene (100 ml.) leaving the potassium salt (4·1 g.), which on grinding with ice-cold concentrated hydrochloric acid (20 ml.) gave the mesoxalic acid methylphenylhydrazone (2·2 g.; 20%), m. p. 109—110° (decomp.), identical with that prepared by method (*a*).

Attempts to prepare mesoxalic acid ethylphenylhydrazone by method (*b*) gave only *glyoxylic acid ethylphenylhydrazone* which crystallised from ethyl acetate–light petroleum in two forms, one with m. p. 114—115° (resolidified, second m. p. 122—123°) (Found: C, 62·1; H, 5·9; N, 14·5%), the other with m. p. 122—123° (decomp.) (Found: C, 62·6; H, 6·4; N, 14·5. $C_{10}H_{12}N_2O_2$ requires C, 62·5; H, 6·2; N, 14·6%).

Mesoxalic acid diphenylhydrazone. This was prepared from dibromomalonic acid (13·1 g.) and *NN*-diphenylhydrazine (9·2 g.) by method (*b*). Acidification of the reaction mixture gave the crude diacid (8·1 g.; 57%), m. p. 145—146° (decomp.). Rapid recrystallisation from ethyl acetate–light petroleum raised the m. p. to 150—151° (decomp.), but an analytically pure specimen could not be obtained as further crystallisation led to decarboxylation and formation of *glyoxylic acid diphenylhydrazone*, m. p. 200—202° (decomp.), identical (m. p. and mixed m. p.) with that prepared as described below.

Glyoxylic acid methylphenylhydrazone. Methylphenylhydrazine (6·1 g.) in ethanol (20 ml.) was added with shaking to dichloroacetic acid (6·45 g.) dissolved in a solution of potassium carbonate (10·8 g.) in water (60 ml.). After being heated under reflux for 4 hr., and allowed to cool overnight, the mixture was extracted with ether (3 × 100 ml.), and the aqueous layer was carefully acidified with hydrochloric acid to give a pale yellow solid (2·8 g.; 31%), m. p. 167—169° (decomp.). Crystallisation from ethyl acetate gave the pure *acid*, m. p. 169—170° (decomp.) (Found: C, 60·8; H, 5·5; N, 15·7. $C_9H_{10}N_2O_2$ requires C, 60·6; H, 5·6; N, 15·7%).

Glyoxylic acid diphenylhydrazone. This was similarly prepared from dichloroacetic acid (6·45 g.), potassium carbonate (10·8 g.), and *NN*-diphenylhydrazine (9·2 g.) in 1 : 1 aqueous ethanol (100 ml.), the mixture being refluxed for 8 hr. After crystallisation from ethyl acetate it (9%) had m. p. 200—202° (decomp.) (Found: C, 70·3; H, 5·3; N, 11·8. $C_{14}H_{12}N_2O_2$ requires C, 70·0; H, 5·0; N, 11·7%).

1-*Methyl*-4-*cinnolone*-3-*carboxylic Acid.*—Ethyl hydrogen mesoxalate methylphenylhydrazone (4 g.) was dissolved in carbon tetrachloride (35 ml.), and 5 ml. of solvent was distilled off to remove traces of water. The cold solution was treated with thionyl chloride (1·2 ml.), and the mixture was refluxed for 2 hr., cooled in ice–salt and filtered. The dark, oily acid chloride isolated from the filtrate was dissolved in dry nitrobenzene (30 ml.), titanium tetrachloride (2 ml.) was added, and the mixture was heated at 95° for 7 hr. A solution of sodium acetate (23 g.) in water (75 ml.) was added and the nitrobenzene was distilled off in steam. The residue was filtered and the filtrate was acidified with concentrated hydrochloric acid and kept in the

[18] Conrad and Reinbach, *Ber.*, 1902, **35**, 1817.

refrigerator for 3 days; a cream solid (1·3 g., 40%), m. p. 242—244°, had then separated. Crystallisation from water (180 ml.) (charcoal) gave *1-methyl-4-cinnolone-3-carboxylic acid*, cream needles (0·8 g.), m. p. 248—249° (Found: C, 58·4; H, 4·0; N, 13·4. $C_{10}H_8N_2O_3$ requires C, 58·8; H, 3·9; N, 13·7%).

The following were prepared similarly: *1-Ethyl-4-cinnolone-3-carboxylic acid* (57%), m. p. 208—212°, which on crystallisation from ethanol gave the pure *acid* (40%) m. p. 213—214° (Found: C, 60·6; H, 4·6; N, 12·85. $C_{11}H_{10}N_2O_3$ requires C, 60·2; H, 4·5; N, 13·1%). *1-Phenyl-4-cinnolone-3-carboxylic acid* (83%), m. p. 275°, crystallised from ethanol giving an analytical sample, m. p. 274—275° (Found: C, 67·8; H, 3·8; N, 10·5. $C_{15}H_{10}N_2O_3$ requires C, 67·6; H, 3·7; N, 10·5%).

In one experiment the intermediate *α-carbethoxyglyoxylyl chloride diphenylhydrazone* was isolated (81%), m. p. 99—108° (Found: Cl, 10·7. $C_{17}H_{15}ClN_2O_3$ requires Cl, 10·7%).

Attempted Decarboxylation of 1-Methyl-4-cinnolone-3-carboxylic Acid.—When the acid was heated alone or in benzophenone (cf. ref. 2), no decarboxylation occurred below *ca.* 265°. After 25 min. in benzophenone at this temperature, no more carbon dioxide was evolved, but only tarry products were isolated, together with unchanged acid.

Attempted Cyclisation of Glyoxylyl Chloride Methylphenylhydrazone.—Glyoxylic acid methylphenylhydrazone (4·4 g.) in dry chloroform (30 ml.) was treated with thionyl chloride (3·0 g., 1·85 ml.), and the mixture was refluxed for 20 min. After the mixture had been evaporated to one-third volume, dry light petroleum (b. p. 60—80°) was added to precipitate glyoxylyl chloride phenylmethylhydrazone (4·5 g., 86%), m. p. 121—126°. The crude acid chloride (3 6 g.) with titanium tetrachloride (3·82 g., 2·2 ml.) in dry nitrobenzene (35 ml.) was heated at 95° for 4·5 hr., and the reaction mixture was worked up in the usual way. Sublimation of the neutral fraction (1·5 g.) at 210—215°/0·01 mm. gave a yellow oil from which no 1-methyl-4-cinnolone could be isolated.

1-Phenyl-4-cinnolone.—(*a*) *By decarboxylation of 1-phenyl-4-cinnolone-3-carboxylic acid.* The powdered acid (3 g.) was added in portions during 20 min. to a stirred refluxing mixture of purified quinoline (10 ml.) and copper chromite (0·04 g.). After a further 5 min. at the b. p. the mixture was cooled, poured into benzene (60 ml.), treated with charcoal and filtered. Chloroform (5 ml.) was added to the filtrate and the clear solution was extracted successively with 2N-sodium hydroxide (2 × 50 ml.) to remove unchanged acid (0·5 g.; m. p. 266—267°), 2N-hydrochloric acid (2 × 60 ml.), and water. The acid extract when diluted and kept at room temperature gave a solid (0·2 g.; m. p. 122—124°) which on crystallisation from aqueous ethanol gave orange plates of 1-phenylisatin (0·1 g.), m. p. 138—139° (Found: C, 76·1; H, 4·5; N, 6·35. Calc. for $C_{14}H_9NO_2$: C, 75·5; H, 4·0; N, 6·3%). (Stolle [19] gave m. p. 138°.) Strong C=O absorption bands were visible at 1609 and 1736 $cm.^{-1}$. The neutral benzene fraction was evaporated to half volume and treated with light petroleum (200 ml.). After removal of some precipitated impurity, the filtrate was evaporated to give a neutral gum (1·05 g.), which at 150—160°/0·07 mm. gave an orange sublimate (0·42 g.). Repeated trituration of this, first with ether–light petroleum then with light petroleum alone gave a buff solid (0·25 g.), m. p. 123—124°, whence crystallisation from aqueous ethanol (20 ml.) (charcoal) gave *1-phenyl-4-cinnolone* (0·1 g.), m. p. 133—134° (decomp.) (Found: C, 75·6; H, 4·8; N, 12·8. $C_{14}H_{10}N_2O$ requires C, 75·6; H, 4·55; N, 12·6%).

Attempted decarboxylation of the acid (mixed with powdered glass) by sublimation at 220—230°/0·02 mm. gave only a sublimate of unchanged acid (m. p. and mixed m. p. 275°).

(*b*) *Attempted preparation by alternative cyclisation route.* *m*-Bromoacetophenone [5] (83 g.) in glacial acetic acid (150 ml.) was treated with bromine (66·8 g.) added dropwise at 50—60°. After being stirred for a further 40 min. the mixture was poured into water and extracted with ether, the extracts were washed successively with water, saturated sodium hydrogen carbonate solution, water, and dried ($MgSO_4$). After removal of the ether the residue was triturated with light petroleum (b. p. 60—80°) to give *m*-bromophenacyl bromide (87 g., 75%), m. p. 42—45°, sufficiently pure for use in the next stage. The phenacyl bromide (16 g.) was stirred with dimethyl sulphoxide (100 ml.) at room temperature for 24 hr.; it was then poured into ice–water, the oil was extracted with ether, and the extracts were washed in water, dried ($MgSO_4$) and evaporated. The semisolid residue was triturated with di-isopropyl ether to give m-*bromophenylglyoxal* (4 g., 33%), m. p. 130—134° (Found: C, 42·9; H, 2·5; Br, 35·4. $C_8H_5BrO_2$

[19] Stollé, *Ber.*, 1913, **46**, 3915.

requires C, 43·2; H, 2·7; Br, 35·0%). Attempts to crystallise it led to formation of glassy products. On a larger scale the product crystallised when poured into ice–water and a 55% yield was obtained. The glyoxal (2·4 g.) was dissolved in ethanol (120 ml.), and 2N-acetic acid (20 ml.) was added, followed by phenylhydrazine (1·08 g.; 1 mol.). After being kept at room temperature for 36 hr., the mixture was poured into water and left at 0° overnight, the solids were filtered off and purified by chromatography on a column of neutral alumina (Woelm) to give m-*bromophenylglyoxal α-monophenylhydrazone*, orange prisms (58%) (from cyclohexane), m. p. 92—94° (Found: C, 55·2; H, 4·0; Br, 26·5; N, 9·4. $C_{14}H_{11}BrN_2O$ requires C, 55·5; H, 3·6; Br, 26·4); N, 9·25%.

The phenylhydrazone (3 g.) was added in dry benzene (40 ml.) under nitrogen to a well stirred suspension of freshly prepared sodamide (10 g.) in refluxing dry benzene (400 ml.). After addition was complete (30 min.), the mixture was refluxed under nitrogen with stirring for 48 hr., then cooled to room temperature and ethanol (15 ml.) was added cautiously dropwise with cooling, followed by water (50 ml.). The benzene layer was separated, washed well with water, dried ($MgSO_4$), and evaporated to give a solid (2·8 g.), which was chromatographed on neutral alumina to give a small amount of orange tar and a main fraction (2·4 g., 80%), m. p. 78—92°, which was unchanged *m*-bromophenylglyoxal phenylhydrazone (m. p. and mixed m. p. 92—93° after recrystallisation).

Anhydro-base of 4-Hydroxy-2-methylcinnolinium Hydroxide.—Methylation of 4-hydroxycinnoline with methyl sulphate [2,5] gave, after repeated crystallisation, the anhydro-base (16%), m. p. 165—166° (lit.,[2] m. p. 165—166°).

Anhydro-base of 6-Chloro-4-hydroxy-2-methylcinnolinium Hydroxide.—(a) *From 6-chloro-4-hydroxycinnoline.* Alkylation of 6-chloro-4-hydroxycinnoline (2 g.) with methyl sulphate as described by Simpson [3] gave the anhydro-base (from benzene), m. p. 221—223° (Simpson [3] gives m. p. 221—222°).

(b) *From 6-chloro-2-methyl-4-methylaminocinnolinium methyl sulphate.* This *quaternary salt* (1·1 g.) obtained [20] from 6-chloro-4-methylaminocinnoline and methyl sulphate at 40°, had m. p. 161—162° (from ethanol) (Found: Cl, 11·0; S, 10·4. $C_{11}H_{14}ClN_3O_4S$ requires Cl, 11·1; S, 10·0%); it was dissolved in hot water (10 ml.) and hot 2N-sodium hydroxide (10 ml.) was added. The mixture was refluxed until evolution of methylamine ceased (30 min.), then filtered while hot, and the buff solid (0·4 g.), m. p. 218—220°, was crystallised from benzene to give the anhydro-base, m. p. 221—223°, identical (m. p. and mixed m. p.) with the sample from (a) above.

Anhydro-base of 2-Benzyl-6-chloro-4-hydroxycinnolinium Hydroxide.—6-Chloro-4-hydroxycinnoline (2·8 g.) was heated under reflux with benzyl chloride (58 ml.) for 1·75 hr. Most of the excess of benzyl chloride was removed *in vacuo* at 90°, and the crystals were filtered off and washed with light petroleum to give the product (2·9 g.), m. p. 192—193°. Crystallisation from ethanol gave the analytical sample, m. p. 192—193° (Found: C, 66·6; H, 4·4; Cl, 12·85. $C_{15}H_{11}ClN_2O$ requires C, 66·5; H, 4·1; Cl, 13·1%). That the product was not the isomeric 4-benzyloxy-6-chlorocinnoline was shown by preparation of the latter from 4,6-dichlorocinnoline and a solution of sodium in excess of benzyl alcohol at 95° for 1 hr. Evaporation of solvent and crystallisation from benzene–light petroleum (b. p. 80—100°) gave *4-benzyloxy-6-chlorocinnoline*, colourless plates, m. p. 118—119° (Found: C, 66·5; H, 4·2; N, 10·4; Cl, 12·7. $C_{15}H_{11}ClN_2O$ requires C, 66·5; H, 4·1; N, 10·3; Cl, 13·1%).

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[20] Lunt, Washbourn, and Wragg, in preparation.