86. *Cinnolines. Part XXVI. Some 4-Cinnolylhydrazines, Their Preparation and Oxidation. Miscellaneous Quinoline Derivatives.*

By K. Schofield and T. Swain.

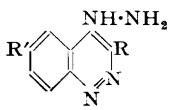
4-*Cinnolylhydrazine* and its 3-*chloro*-, 6-*chloro*-, and 6-*bromo*-derivatives are described. Except for the 3-chloro-compound, these are oxidised by aqueous copper sulphate to the corresponding *cinnolines*. 4-*Phenylhydrazino*- and 3-*chloro*-4-*phenylhydrazino-cinnoline* have been prepared. Attempts to prepare derivatives of 3-aminocinnoline are mentioned, and miscellaneous quinoline derivatives reported.

From the reaction between hydrazine and 4-chloroquinaldine Backeberg and Friedmann (*J.*, 1938, 972) obtained either of two products, according to the conditions. Condensation in hot alcohol gave 4-quinaldylhydrazine, whilst reaction at a higher temperature, under pressure, gave an isomeric compound which the authors suggested to be 3 : 4-diaminoquinaldine. Various pieces of evidence made this structure uncertain, but only after this work had begun was it completely disproved (Koenigs and Freund, *Ber.*, 1947, **80**, 143).

Since we desired to prepare 3 : 4-diaminocinnolines, in the light of Backeberg and Friedmann's suggestion it seemed of interest to examine the reaction between 4-chlorocinnolines and hydrazine. Further, 4-cinnolylhydrazines offered the possibility of obtaining, by oxidation, hitherto unknown derivatives of cinnoline unsubstituted at $C_{(4)}$.

4-Chlorocinnoline reacted with hydrazine in alcohol much more slowly and less vigorously than did 4-chloroquinazoline (Dewar, *J.*, 1944, 619; we have repeated the reaction for

comparative purposes). Though only qualitative, the observation is in agreement with the calculations of Longuet-Higgins and Coulson (*J.*, 1949, 971), which indicate that $C_{(4)}$ in quinazoline should be more susceptible to nucleophilic attack than the same position in cinnoline. The product of the reaction was a deep orange-coloured solid, m. p. 293—294° (decomp.), but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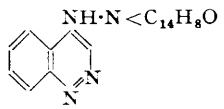
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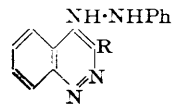
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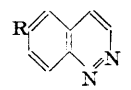
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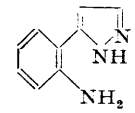
(V.)

after two crystallsations from alcohol its m. p. changed to 226—227° (decomp.). The high-melting form was produced in a reaction carried out under pressure. In view of the behaviour of 4-chloroquinaldine, it was at first thought that isomerisation was involved, but experiment showed that the substances were merely different crystalline forms of 4-*cinnolylhydrazine* (I; R = R′ = H). Thus, both gave the same *hydrochloride*, and the same *diacetyl* derivative. Any possibility that the low-melting form might be 3 : 4-diaminocinnoline was removed by the formation from it of a *monoformyl* derivative, and of a *product* $C_{22}H_{14}ON_4$ (II) with phenanthraquinone. Finally, both substances gave cinnoline when oxidised with aqueous copper sulphate.

3-*Chloro-* (I; R = Cl, R′ = H), 6-*chloro-* (I; R = H, R′ = Cl), and 6-*bromo-4-cinnolylhydrazine* (I; R = H, R′ = Br) were prepared in the same way, but none of these showed polymorphism. Replacement of hydrazine by phenylhydrazine in the reaction gave 4-*phenylhydrazino-* (III; R = H), and 3-*chloro-4-phenylhydrazino-cinnoline* (III; R = Cl).

On oxidation with aqueous copper sulphate 3-chloro-4-cinnolylhydrazine underwent violent decomposition and no recognisable product was isolated. In contrast 6-chloro- and 6-bromo-4-cinnolylhydrazine readily gave 6-*chloro-* (IV; R = Cl), and 6-*bromo-cinnoline* (IV; R = Br). Dewar (*loc. cit.*) reported that 4-quinazolylhydrazine was unaffected by acid or neutral copper sulphate, but was oxidised by Fehling's solution, some quinazoline being formed. In our hands, aqueous copper sulphate oxidised 4-quinazolylhydrazine to an unidentified product, the *picrate* of which gave analyses in rough agreement with those required for a hydroxyquinazoline derivative, but which appears to differ from 4-hydroxyquinazoline picrate (Bogert and Hand, *J. Amer. Chem. Soc.*, 1902, **24**, 1031).

A few attempts to introduce an amino-group by replacement of halogen in 3-halogenocinnolines failed. 3-Bromo-4-hydroxycinnoline gave no recognisable product when heated with aqueous ammonia in the presence of copper sulphate. 3-Bromo-4-hydroxycinnoline was the only isolable product from the reaction between 4-chloro-3-bromocinnoline and alcoholic ammonia under pressure, but in similar circumstances 3 : 4-dichlorocinnoline gave 3-*chloro-4-aminocinnoline*, identical with a specimen prepared from 3-chloro-4-phenoxycinnoline. The use of aqueous ammonia in this case gave a mixture of the 4-amino-compound and 3-chloro-4-hydroxycinnoline. With either aqueous or alcoholic ammonia 4 : 6-dichlorocinnoline gave only 6-chloro-4-hydroxycinnoline. The erratic nature of these results, and the experience of Keneford, Schofield, and Simpson (*J.*, 1948, 358) and of Baker (*J.*, 1948, 1713) with reactions of this type, suggest that they would merit closer examination.

Backeberg and Friedmann (*loc. cit.*), by treating 4-chloroquinoline with hydrazine under pressure, obtained a product, m. p. 129°, which they supposed to be 3 : 4-diaminoquinoline, but which, in view of the work of Koenigs and Freund (*loc. cit.*), must now be regarded as (V). Approaching the problem before the results of Koenigs and Freund appeared, we found it necessary first to compare Backeberg and Friedmann's product directly with authentic specimens of 4-quinolylhydrazine and 3 : 4-diaminoquinoline, which they had not done. 4-Quinolylhydrazine was described by Brydowna (*Rocz. Chem.*, 1932, **12**, 88; only an abstract was available to us), but in trying to repeat the preparation, whilst 4-*quinolylhydrazine hydrochloride* was readily obtained, attempts to form the free base gave a white solid, m. p. 135—140° (Brydowna, *loc. cit.*, gives m. p. 140—142°), which rapidly decomposed in air (Knueppel, *Annalen*, 1900, **310**, 82, reported that 6-quinolylhydrazine is likewise unstable). 3 : 4-Diaminoquinoline was obtained by Renshaw, Friedman, and Gajewski (*J. Amer. Chem. Soc.*, 1939, **61**, 3322) by reducing 3-amino-4-phenylazoquinoline, and by the action of ammonia on 3-bromo-4-aminoquinoline. We have now prepared it from 3-nitro-4-aminoquinoline, and characterised it as its *hydrochloride* and *diacetyl* derivative.

Experimental.

(M. p.s are uncorrected.)

4-Cinnolylhydrazine.—(*a*) (i) 4-Chlorocinnoline (2 g.) and hydrazine (2 c.c.; 90%) in alcohol (50 c.c.) were left for 4 days at room temperature. (Under similar conditions 4-chloroquinazoline reacted immediately, with evolution of heat and precipitation of the product.) The mixture of yellow crusts and hydrazine hydrochloride formed was collected and washed with water, giving a deep orange crystalline solid (1·77 g., 91%), m. p. 293—294° (decomp.) (the substance turned deep red at 200—210°). The use of 50% hydrazine hydrate gave slightly lower yields (81%).

(ii) 4-Chlorocinnoline (0·76 g.) and hydrazine hydrate (1·5 c.c.; 90%) were heated for 22 hours at 150—160° in a sealed tube. The product (0·70 g.; m. p. 150—160°) on crystallisation from alcohol gave deep-red leaflets (0·22 g.), m. p. 290—291° (decomp.) (changing colour as before), which did not depress the m. p. of the product from (i).

(*b*) One crystallisation from alcohol of the product from (i) gave bright orange plates, m. p. 296—297°; a second crystallisation from the same solvent gave orange plates, m. p. 224—226° (decomp.) (becoming deep red at 180°). Further crystallisation gave *4-cinnolylhydrazine*, m. p. 226—227° (decomp.) (Found: C, 59·7; H, 5·1; N, 34·7. $C_8H_8N_4$ requires C, 59·9; H, 5·0; N, 34·9%). Either the high- or the low-melting form of the compound dissolved in hot concentrated hydrochloric acid to give very small white crystals of a hydrochloride, m. p. 244—245° (not analysed). Either form when treated with boiling acetic anhydride gave the *diacetyl* derivative, which formed white crystals, m. p. 208—209°, from alcohol (Found: C, 58·6; H, 4·9. $C_{12}H_{12}O_2N_4$ requires C, 58·9; H, 4·9%). Hot anhydrous formic acid likewise gave the *monoformyl* derivative, which formed yellow plates, m. p. 229—230°, from hot water (Found: C, 57·4; H, 4·6. $C_9H_8ON_4$ requires C, 57·4; H, 4·3%). When treated with phenanthraquinone in boiling acetic anhydride, 4-cinnolylhydrazine gave a *monohydrazono*-derivative, which formed glistening red microcrystals, m. p. 267—268°, from alcohol (Found: C, 74·6; H, 4·3; N, 15·0. $C_{22}H_{14}ON_4$ requires C, 75·4; H, 4·0; N, 15·9%).

3-Chloro-4-cinnolylhydrazine.—As in the above case, 3:4-dichlorocinnoline (1·26 g.) and hydrazine (1·5 c.c.; 90%), in alcohol (20 c.c.), gave a product [1·10 g.; m. p. 255° (decomp.)] which formed orange leaflets of *3-chloro-4-cinnolylhydrazine*, m. p. >300° (becoming deep red at 200—220°) (Found: C, 49·4; H, 3·7. $C_8H_7N_4Cl$ requires C, 49·4; H, 3·6%).

6-Chloro-4-cinnolylhydrazine.—In the same way, from 4:6-dichlorocinnoline (1·85 g.), hydrazine hydrate (2 c.c.), and alcohol (120 c.c.), a product was obtained (0·65 g.; m. p. >320°) which formed orange yellow crystals of *6-chloro-4-cinnolylhydrazine*, m. p. >320° (turning deep red at 220°), from alcohol (Found: C, 49·1; H, 3·7%).

6-Bromo-4-cinnolylhydrazine.—4-Chloro-6-bromocinnoline (2·25 g.) likewise gave a product (1·93 g.; m. p. >300°), which was digested with alcohol and reprecipitated from hydrochloric acid solution with ammonia, forming orange microcrystals of *6-bromo-4-cinnolylhydrazine*, m. p. >300° (becoming deep red at 220°) (Found: C, 41·1; H, 3·3. $C_8H_7N_4Br$ requires C, 40·2; H, 2·9%).

Oxidation of 4-Cinnolylhydrazines.—(i) 4-Cinnolylhydrazine (0·2 g.) was heated under reflux with water (2 c.c.), a solution of copper sulphate (4 c.c.; 10%) was added dropwise during 5 minutes (a vigorous reaction ensued), and the mixture was then boiled for ½ hour. Filtration, basification of the filtrate, and ether-extraction removed an oil (0·09 g.). Dissolved in ether (5 c.c.) and treated with picric acid [0·20 g., in benzene (2 c.c.)], this gave a precipitate which formed khaki leaflets, m. p. 191·5—192·5°, from alcohol (Found: C, 47·2; H, 3·7. Calc. for $C_{14}H_9O_7N_5$: C, 46·8; H, 2·5%), identical with cinnoline picrate (Busch and Rast, *Ber.*, 1897, **30**, 521).

(ii) 6-Chloro-4-cinnolylhydrazine (0·5 g.) under the same conditions reacted with moderate vigour and yielded a buff-coloured solid, crystallising from ether–ligroin (b. p. 60—80°) as pale brown lustreless prisms of *6-chlorocinnoline* (0·14 g.), m. p. 119—120° (Found: C, 58·8; H, 3·5. $C_8H_5N_2Cl$ requires C, 58·4; H, 3·1%).

(iii) 6-Bromo-4-cinnolylhydrazine (2 g.) likewise gave *6-bromocinnoline* (0·47 g.), which formed pale buff-coloured needles from ether–ligroin (b. p. 60—80°), m. p. 129—130° (Found: C, 46·9; H, 2·8. $C_8H_5N_2Br$ requires C, 46·0; H, 3·2%).

(iv) Under these conditions 3-chloro-4-cinnolylhydrazine underwent violent oxidation, and the tarry product could neither be crystallised nor converted into a picrate.

Oxidation of 4-Quinazolylhydrazine.—4-Quinazolylhydrazine (0·2 g.), oxidised as above, gave an oily solid which, treated with picric acid (0·1 g.), in alcohol (4 c.c.), gave a *picrate* (0·14 g.), forming yellow microcrystals, m. p. 151—152°, from alcohol (Found: C, 45·4; H, 2·5; N, 16·4. $C_{14}H_9O_8N_5$ requires C, 44·8; H, 2·4; N, 18·6%) (Bogert and Hand, *loc. cit.*, give m. p. 204—205° for 4-hydroxyquinazoline picrate).

4-Phenylhydrazinocinnoline.—A solution of 4-chlorocinnoline (1·9 g.), alcohol (45 c.c.), and phenylhydrazine (3 g.) was left for 3 days at room temperature, filtered from phenylhydrazine hydrochloride, the alcohol removed *in vacuo*, and the tarry residue washed with water and dried on a porous plate. After repeated extraction with ether and crystallisation from alcohol, the solid gave yellow rhombs of *4-phenylhydrazinocinnoline* (0·52 g.), m. p. 238° (decomp.) (Found: 64·1; H, 5·0. $C_{14}H_{12}N_4,1\frac{1}{2}H_2O$ requires C, 63·9; H, 5·5%).

3-Chloro-4-phenylhydrazinocinnoline.—3:4-Dichlorocinnoline (0·5 g.) and phenylhydrazine (0·75 g.), in alcohol (20 c.c.), were left for 6 days at room temperature, and then worked up as above. Crystallisation of the crude product from dilute alcohol gave lustreless brown leaflets (0·39 g.) of *3-chloro-4-phenylhydrazinocinnoline*, m. p. 134—135° (Found: C, 62·5; H, 4·4. $C_{14}H_{11}N_4Cl$ requires C, 62·1; H, 4·1%).

4-Quinolylhydrazine Hydrochloride.—4-Chloroquinoline (1 g.), hydrazine hydrate (1 c.c.; 90%), and alcohol (10 c.c.) were heated under reflux for 8 hours in an atmosphere of nitrogen. Removal of the alcohol, extraction with ether, concentration of the extract to *ca.* 20 c.c., and drying (Na_2SO_4), followed by passage of dry hydrogen chloride, gave a granular solid. Recrystallisation from dilute alcohol

provided white microcrystals (0·21 g.) of *4-quinolylhydrazine hydrochloride*, m. p. 300—301° (Found : C, 55·1; H, 5·3. $C_9H_9N_3$,HCl requires C, 55·3; H, 5·2%). In other experiments the free base was isolated as a white solid, m. p. 135—140° (Brydowna, *loc. cit.*, gives m. p. 140—142°), which decomposed in a few hours in the air to a black mass with a strong quinoline-like smell.

3 : 4-*Diaminoquinoline*.—(*a*) 3-Nitro-4-aminoquinoline was obtained by a method essentially similar to that since described by Albert *et al.* (*J.*, 1948, 1284), and also from 3-nitro-4-phenoxyquinoline (Schofield and Swain, *J.*, 1949, 1367) as follows. The phenoxy-compound (0·5 g.) was added to ammonium acetate (previously heated at 180°) at 160°, and the temperature raised to 210° during 8 minutes. After 10 minutes at this temperature the mixture was cooled and diluted with water, and the precipitate (0·30 g.) crystallised from alcohol. 3-Nitro-4-aminoquinoline formed yellow needles, m. p. 261—262° (Found : C, 57·2; H, 3·7. Calc. for $C_9H_7O_2N_3$: C, 57·3; H, 3·8%).

(*b*) 3-Nitro-4-aminoquinoline (0·81 g.) in concentrated hydrochloric acid (16 c.c.) was treated with stannous chloride (4 g.) in the same solvent (10 c.c.) at 95°, and the solution heated at this temperature for 2 hours. The mixture was basified with concentrated sodium hydroxide solution, extracted with ether, the extract washed with 6N-sodium hydroxide solution and water, and, after drying (Na_2SO_4), the ether was removed. Crystallisation of the almost pure residue (0·6 g.) from water gave 3 : 4-diaminoquinoline in two forms : one, solvent-free brown prisms, m. p. 171—172° (Found : C, 67·6; H, 5·7. Calc. for $C_9H_9N_3$: C, 67·9; H, 5·7%) (Renshaw *et al.*, *loc. cit.*, give m. p. 174°), and the other, lustreless pale brown needles, m. p. 93—94° (Found : C, 63·6; H, 5·6; N, 24·7. $C_9H_9N_3,\frac{1}{2}H_2O$ requires C, 64·3; H, 5·9; N, 24·9%). The diamine, m. p. 171—172°, when treated in ether with dry hydrogen chloride, gave very small white crystals of a hydrochloride, m. p. 298—299° (not analysed). Boiling acetic anhydride converted the diamine into a *diacetyl* derivative, which crystallised from dilute methanol in small white needles, m. p. 230—231° (Found : C, 62·2; H, 6·3. $C_{13}H_{13}O_2N_3,H_2O$ requires C, 62·3; H, 5·6%).

3-*Chloro*-4-*aminocinnoline*.—(*a*) 3-Chloro-4-phenoxycinnoline (1·5 g.) (see previous paper) was added in one portion to ammonium acetate (9 g.; previously heated to 180°) at 160°. Dilution with water gave a precipitate of 3-chloro-4-hydroxycinnoline (0·19 g.). Basification of the filtrate from this, with ammonia (*d* 0·88), gave a precipitate (0·57 g.) of *3-chloro-4-aminocinnoline*, which formed fine white needles, m. p. 228—229°, from alcohol (Found : C, 53·2; H, 3·4. $C_8H_6N_3Cl$ requires C, 53·5; H, 3·4%).

(*b*) 3 : 4-Dichlorocinnoline (0·5 g.) in saturated alcoholic ammonia (10 c.c.) was heated for 22 hours at 150—160° in a sealed tube. Removal of the alcohol from the product, and crystallisation from dilute alcohol, gave 3-chloro-4-aminocinnoline (0·33 g.), identical with the above.

3 : 4-Dichlorocinnoline (0·5 g.), treated in the same way with aqueous ammonia (5 c.c.; *d* 0·88), gave 3-chloro-4-aminocinnoline (0·08 g.) and 3-chloro-4-hydroxycinnoline (0·23 g.).

Under the above conditions, with either alcoholic or aqueous ammonia, both 4-chloro-3-bromo- and 4 : 6-dichloro-cinnoline gave only the 4-hydroxy-compounds.

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