132. *Fungicidal Activity and Chemical Constitution. Part V.*[1] *Synthesis of Some Substituted Quinolines.*

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The preparation of 6-hydroxy-5-*n*-pentyl- and 7-chloro-8-hydroxy-5-*n*-pentyl-quinoline is described.

The fungistatic activity of the 5-*n*-alkyl-8-hydroxyquinolines, prepared earlier [1] in an attempt to improve the activity of 8-hydroxyquinoline against the mycelium of *Aspergillus niger* van Tiegh.,[2] followed the pattern normally encountered in such an homologous series.[3] It rose to a maximum at a chain length of 5 or 6 carbon atoms, though the addition of Cu^{2+} markedly reduced the activity.[4] In order to confirm the rôle played by chelation in the fungicidal activity of 8-hydroxy-5-*n*-pentylquinoline, it was decided to prepare and test the isomeric 6-hydroxy-5-*n*-pentylquinoline, which should possess comparable lipoid solubility whilst being incapable of chelation with heavy metals.

Fries migration of *m*-chlorophenyl valerate at 165° gave butyl 4-chloro-2-hydroxyphenyl ketone as the main product, the orientation being established by oxidation with potassium permanganate to 4-chloro-2-hydroxybenzoic acid. The isomeric butyl 2-chloro-4-hydroxyphenyl ketone, oxidisable to 2-chloro-4-hydroxybenzoic acid, is also formed, in greater amount at lower temperature as in the case of the Fries reaction of *m*-tolyl valerate.[5] There was no formation of butyl 2-chloro-6-hydroxyphenyl ketone, which would involve preferential substitution of a sterically hindered *ortho*-position.

Clemmensen reduction of butyl 4-chloro-2-hydroxyphenyl ketone gave 5-chloro-2-*n*-pentylphenol which on nitration in acetic acid solution gave a mixture of two mononitrophenols separable by fractional distillation. In an attempted Skraup reaction with the amine obtained by reduction of the lower boiling nitrophenol there was high recovery of

[1] Part IV, Woodcock, *J.*, 1955, 4391.
[2] Byrde and Woodcock, *Ann. Appl. Biol.*, in the press.
[3] Ferguson, *Proc. Roy. Soc.*, 1939, *B*, **127**, 387.
[4] Byrde and Woodcock, *Nature*, 1957, **179**, 539.
[5] Blatt, *Org. Reactions*, Vol. I, p. 342.

unchanged amine, whilst similar treatment of the amine from the second nitration product gave 8-chloro-6-hydroxy-5-*n*-pentylquinoline, which was reduced to the required 6-hydroxy-5-*n*-pentylquinoline by hydrogen in the presence of palladised charcoal.

In order to examine the effect of halogen substitution on fungistatic activity, 7-chloro-8-hydroxy-5-*n*-pentylquinoline was prepared by a similar route from *o*-chlorophenyl valerate.

When tested against the mycelium of *A. niger*, 6-hydroxy-5-*n*-pentylquinoline was considerably less toxic than 8-hydroxy-5-*n*-pentylquinoline; introduction of a nuclear chlorine atom had little effect on the toxicity of the latter hydroxyquinoline. It is hoped that full discussion of the biological results will be published elsewhere.[2]

Experimental

Butyl 4-Chloro-2-hydroxyphenyl Ketone.—*m*-Chlorophenyl valerate [38·4 g.; prepared by heating *m*-chlorophenol (21 g.) with *n*-valeryl chloride (20 ml.) until the evolution of hydrogen chloride ceased] was stirred at 165° during gradual addition of anhydrous aluminium chloride (28 g.) and then heated for a further 1 hr. After addition of ice-cold hydrochloric acid, the product was extracted with ether, the ethereal solution washed with dilute hydrochloric acid and dried (Na_2SO_4), and the solvent removed. Distillation of the residue gave unchanged ester (5 g.) and two fractions, b. p. 160—164°/12 mm. (19 g.) (Found: C, 62·0; H, 6·0. $C_{11}H_{13}O_2Cl$ requires C, 62·1; H, 6·1%), and b. p. 190—192°/2 mm. (5 g.). The yield of the lower-boiling fraction, which is the required *ketone* was considerably reduced by a lower temperature in the Fries migration. The lower-boiling fraction (1 g.) was refluxed in acetone (20 ml.) for 4 hr. with powdered potassium permanganate (7 g., added in two portions). After decolorisation with sulphur dioxide, acidic material was isolated from an ethereal extract by using sodium hydrogen carbonate. It crystallised from aqueous methyl alcohol in needles, m. p. 212—213° undepressed by admixture with an authentic specimen of 4-chloro-2-hydroxybenzoic acid.[6] Similar oxidation of the higher-boiling fraction gave 2-chloro-4-hydroxybenzoic acid, m. p. 158—159°, identical with an authentic specimen.[7]

Nitration of 5-Chloro-2-n-pentylphenol.—A solution of the above phenol (46 g.) in acetic acid (92 ml.) was stirred at 0—5° during the dropwise addition of 33% v/v nitric acid (31·5 ml.). After a further hour's stirring, water (150 ml.) was added and the whole extracted with ether, washed with water and sodium hydrogen carbonate solution, and dried (Na_2SO_4). Removal of the solvent and distillation gave fractions (A) (20 g.), b. p. 145—146°/0·5 mm., and (B) (22 g.), b. p. 200—202°/0·5 mm. [Found (A): C, 54·1; H, 6·2; N, 5·7. Found (B): C, 53·9; H, 6·0; N, 5·7. $C_{11}H_{14}O_3NCl$ requires C, 54·2; H, 5·75; N, 5·75%].

2-Amino-3-chloro-6-n-pentylphenol.—The product (A) above (23·5 g.) was shaken in tetrahydrofuran (50 ml.) and with Raney nickel in hydrogen until uptake ceased. After removal of the catalyst on a centrifuge, the solvent was distilled off and the residue triturated with light petroleum (b. p. 40—60°). The solid *product* (8·9 g.) crystallised from light petroleum (b. p. 60—80°) in prismatic plates, m. p. 84—85° (Found: C, 62·0; H, 7·4; N, 6·8. $C_{11}H_{16}ONCl$ requires C, 61·8; H, 7·5; N, 6·55%). An attempted Skraup reaction with this amine as described below gave a product which crystallised from ethyl alcohol–ether in prisms, m. p. 211—212°, undepressed by admixture with 2-amino-3-chloro-6-*n*-pentylphenol hydrochloride, m. p. 212—213°.

4-Amino-5-chloro-2-n-pentylphenol.—The nitration product (B) was reduced as described above for product (A). The *amine* crystallised from aqueous methyl alcohol in plates, m. p. 149—150° (Found: C, 62·2; H, 7·4; N, 6·8%).

8-Chloro-6-hydroxy-5-n-pentylquinoline.—4-Amino-5-chloro-2-*n*-pentylphenol (8·6 g.), concentrated sulphuric acid (9·6 ml.), and glycerol (8 ml.) were mixed and heated at 165° for 0·5 hr., then arsenic pentoxide (8·6 g.) was added and heating continued for a further 4 hr. The cooled mixture was diluted with water, excess of 10% aqueous sodium hydroxide added, the whole filtered, and the filtrate acidified with acetic acid. The product was extracted with ether, and the ethereal solution washed with water and sodium hydrogen carbonate solution and dried (Na_2SO_4). After removal of the solvent the residue separated from aqueous methyl

[6] Sheehan, *J. Amer. Chem. Soc.*, 1948, **70**, 1665.
[7] Hodgson and Jenkinson, *J.*, 1927, 1740.

alcohol and finally from ether–light petroleum (b. p. 40—60°) as a microcrystalline powder (1·4 g.), m. p. 124° (Found: C, 67·0; H, 6·7; N, 5·8. $C_{14}H_{16}ONCl$ requires C, 67·3; H, 6·4; N, 5·6%). The *hydrochloride*, prepared by treating an ethereal solution of the base with dry hydrogen chloride, crystallised from ethyl alcohol–ether in prisms, m. p. 205—206° (Found: C, 58·9; H, 5·8; N, 5·1. $C_{14}H_{17}ONCl_2$ requires C, 58·75; H, 5·9; N, 4·9%).

6-Hydroxy-5-n-pentylquinoline.—8-Chloro-6-hydroxy-5-*n*-pentylquinoline (1·2 g.) was shaken in a solution of sodium hydroxide (0·24 g.) in water (5 ml.), and for 4 hr. at 100—120° with palladised charcoal (0·6 g.) under hydrogen at 6 atm. On cooling, the filtered solution was acidified with acetic acid, extracted with ether, washed with water, and dried (Na_2SO_4). Treatment of this dry ethereal solution with hydrogen chloride gave the *hydrochloride* which separated from ethyl alcohol–ether as a buff-coloured powder (0·4 g.), m. p. 272—274° (Found: C, 66·9; H, 7·2; N, 5·9. $C_{14}H_{18}ONCl$ requires C, 66·8; H, 7·2; N, 5·6%). This hydrochloride was dissolved in a slight excess of dilute sodium hydroxide and acidified with acetic acid, and the *base* extracted with ether. It crystallised from ether–light petroleum (b. p. 60—80°) in prisms, m. p. 124—125° (Found: C, 77·7; H, 8·2; N, 6·4. $C_{14}H_{17}ON$ requires C, 78·1; H, 7·9; N, 6·5%).

Butyl 3-Chloro-4-hydroxyphenyl Ketone.—*o*-Chlorophenyl valerate (26·6 g.) was stirred at 110° during gradual addition of finely powdered aluminium chloride (30 g.) and for a further 2 hr. Isolation of the product as in the previous Fries reaction gave fractions, b. p. 118—120°/10 mm. (5·3 g.) and b. p. 180—184°/4 mm. (18·7 g.). Crystallisation of the latter from ether–light petroleum (b. p. 40—60°) gave rhombic plates, m. p. 97—98° (Found: C, 62·2; H, 6·2. Calc. for $C_{11}H_{13}O_2Cl$: C, 62·1; H, 6·1%). Nguyen-Hoán and Buu-Hoï [8] give m. p. 97°.

2-Chloro-5-n-pentylphenol.—The above ketone (25 g.) was reduced with amalgamated zinc and hydrochloric acid. The product (18·3 g.), isolated as previously described, had b. p. 138—140°/15 mm. (Found: C, 66·3; H, 7·5. Calc. for $C_{11}H_{15}OCl$: C, 66·5; H, 7·55%). Klarman, Shternov, and Gates,[9] who prepared this compound by chlorination of 4-*n*-pentylphenol with sulphuryl chloride, give b. p. 115—116°/2 mm.

2-Chloro-6-nitro-4-n-pentylphenol.—A solution of the preceding phenol (18·3 g.) in acetic acid (37 ml.) was nitrated as described for the isomeric compound. Distillation of the *product* gave a pale yellow liquid (16·8 g.), b. p. 165—170°/6 mm. (Found: C, 54·5; H, 6·2; N, 5·7. $C_{11}H_{14}O_3NCl$ requires C, 54·2; H, 5·75; N, 5·75%).

2-Amino-6-chloro-4-n-pentylphenol.—Reduction of the corresponding nitrophenol as described for the isomer gave a colourless *amine* (10 g.), b. p. 140—150°/2 mm. Crystallisation from ether–light petroleum (b. p. 40—60°) gave plates, m. p. 57—58° (Found: C, 62·1; H, 7·7; N, 6·7. $C_{11}H_{16}ONCl$ requires C, 61·8; H, 7·5; N, 6·55%).

7-Chloro-8-hydroxy-5-n-pentylquinoline.—The preceding amine (4·3 g.), sulphuric acid (4·8 ml.; *d* 1·84), and glycerol (4 ml.) were heated at 160° for 0·5 hr. and then for a further 4 hr. after addition of arsenic pentoxide (4·3 g.). On cooling, water was added and the *product* isolated by continuous extraction with chloroform. It crystallised from aqueous methyl alcohol in pale yellow monoclinic prisms (0·5 g.), m. p. 107—107·5° (Found: C, 67·4; H, 6·5; N, 5·8. $C_{14}H_{16}ONCl$ requires C, 67·3; H, 6·4; N, 5·6%).

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[8] Nguyen-Hoán and Buu-Hoï, *Compt. rend.*, 1947, **224**, 1363.
[9] Klarman, Shternov, and Gates, *J. Amer. Chem. Soc.*, 1933, **55**, 2576.