Fungicidal Activity and Chemical Constitution. Part IV. Synthesis of* 5-n-*Alkyl*-8-*hydroxyquinolines.*

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Eleven new analogues of 8-hydroxyquinoline have been prepared in an attempt to improve the fungicidal activity.

The antibacterial properties of 8-hydroxyquinoline (" oxine ") and its derivatives are well known [see especially Albert *et al.*, Goldacre, and Balfour, *Brit. J. Exp. Path.*, 1947, **28**, 69; 1950, **31**, 425; *Biochem. J.*, 1947, **41**, 534; *J.*, 1952, 4985; 1954, 505; Shchukina and Savitskaya, *J. Gen. Chem.* (*U.S.S.R.*), 1952, **22**, 1218; Urbanski, Slopek, and Venulet, *Nature*, 1951, **169**, 29]. It is only recently that their fungicidal action has been examined: Mason (*Phytopathology*, 1948, **38**, 740) tested eleven derivatives against *Stemphylium sarcinaeforme* and showed that chlorine or bromine in position 5 or 7 decreased the toxicity, but there has been no other systematic work.

The increase in fungistatic action due to long aliphatic side-chains in tetrahydroglyoxaline (Wellman and McCallan, *Contribn. Boyce Thompson Inst.*, 1946, **14**, 151) and tetrahydropyrimidine (Rader, Monroe, and Whetstone, *Science*, 1952, **115**, 124) prompted the present work. Of the 5-*n*-alkyl-8-hydroxyquinolines only the methyl (Noelting and Trautmann, *Ber.*, 1890, **23**, 3654) and the propyl compound (Albert and Magrath, *Biochem. J.*, 1947, **41**, 534) have been previously prepared. The appropriate phenyl ester subjected to a Fries migration at 100—140° with anhydrous aluminium chloride gave a mixture of alkyl *o*- and *p*-hydroxyphenyl ketones separable by fractional distillation. Clemmensen reduction of the *para*-isomers gave the *p*-*n*-alkylphenols, the higher homologues often requiring prolonged treatment. Nitration of the *p*-*n*-alkylphenols in glacial acetic acid gave the 2-nitro-compounds, which were reduced in tetrahydrofuran in the presence of Raney nickel. In the final Skraup reaction arsenic pentoxide was the most successful of the oxidising agents used though the yields were poor throughout in contrast to those obtained by Vorozhtsov and Troshchenko [*J. Gen. Chem.* (*U.S.S.R.*), 1938, **8**, 431] for 8-hydroxy-5-phenyl- (95%) and by McMaster and Bruner (*J. Amer. Chem. Soc.*, 1935, **57**, 1697) for 5-benzyl-8-hydroxy-quinoline (86%). The vulnerability of the lengthy alkyl substituent to the strong oxidising conditions present in the Skraup mixture which possibly accounts for the low yields appears to be even greater when a branched chain is present. Thus 2-amino-4-*tert.*-butylphenol gave only 8-hydroxyquinoline in a Skraup reaction with arsenic pentoxide though Coates, Cook, Heilbron, Hey, Lambert, and Lewis (*J.*, 1943, 409) prepared 5-*tert.*-butyl-8-pyridylquinoline in a similar reaction by using sodium *m*-nitrobenzenesulphonate. Niederl (U.S.P. 2,483,838) reported the preparation of 8-hydroxy-5-(1 : 1 : 3 : 3-tetramethylbutyl)quinoline, m. p. 73°, from 2-amino-4-(1 : 1 : 3 : 3-tetramethylbutyl)phenol using picric acid, but this and various other oxidising agents in our hands gave only 8-hydroxyquinoline, m. p. 73°, as the final product.

The results of the biological testing by Dr. R. J. W. Byrde will be described elsewhere.

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Experimental

p-*Hydroxyphenyl Nonyl Ketone.*—The preparation of this compound, not previously described, exemplifies the conditions used in the Fries reaction. Phenyl decanoate [30 g.; prepared by heating phenol (12 g.) with decanoyl chloride (25 g.) until the evolution of hydrogen chloride ceased] was stirred at 110—120° (for higher ketones, 130—140°) during the gradual addition of powdered anhydrous aluminium chloride (18 g.), and then heated for a further 1 hr. After the addition of ice-cold hydrochloric acid, the product was extracted with ether, the ethereal solution washed with dilute hydrochloric acid and then water and dried, and the solvent removed. Distillation of the residue gave fractions, b. p. 150—160°/0·5 mm. and 160—200°/0·5 mm. Crystallisation of the latter from light petroleum (b. p. 60—80°) gave rhombic plates, m. p. 64—65° (Found: C, 77·6; H, 9·5. $C_{16}H_{24}O_2$ requires C, 77·4; H, 9·7%).

p-*Decylphenol.*—The above *ketone* (12·7 g.) was refluxed with amalgamated zinc (65 g.) and hydrochloric acid (65 ml.; *d* 1·16) for 48 hr., additional acid being added at 12-hourly intervals. On cooling, the product was extracted with ether, and the ethereal solution washed with dilute

4-n-*Alkyl-2-nitrophenols.*

Alkyl	Nitration temp.	M. p. or b. p.	Solvent	Found (%) C	H	N	Formula	Required (%) C	H	N
C_6H_{13}...	5—10°	135—140°/2 mm.	—	64·4	7·6	6·0	$C_{12}H_{17}O_3N$	64·6	7·6	6·3
C_8H_{17}...	10	32—33	B	67·3	8·4	5·5	$C_{14}H_{21}O_3N$	66·9	8·4	5·5
C_9H_{19}...	5—10	49—50	MeOH	67·9	8·5	5·3	$C_{15}H_{23}O_3N$	67·9	8·7	5·3
$C_{10}H_{21}$...	10	45—46	B	68·5	9·0	5·0	$C_{16}H_{25}O_3N$	68·8	9·0	5·0
$C_{12}H_{25}$...	10—20	55—56	MeOH	70·2	9·5	4·5	$C_{18}H_{29}O_3N$	70·35	9·4	4·6
$C_{14}H_{29}$...	10—20	62	MeOH	71·3	9·8	4·2	$C_{20}H_{33}O_3N$	71·6	9·9	4·2
$C_{18}H_{37}$...	30—40	72	MeOH	73·3	10·5	3·6	$C_{24}H_{41}O_3N$	73·7	10·5	3·6

B = light petroleum (b. p. 40—60°).

4-n-*Alkyl-2-aminophenols.*

Alkyl	M. p.	Solvent	Found (%) C	H	N	Formula	Required (%) C	H	N
C_4H_9	142—143°	A	69·8	8·0	10·2	$C_{10}H_{15}ON$	70·1	8·0	10·2
C_5H_{11}	135—136	A	73·9	9·4	7·8	$C_{11}H_{17}ON$	73·7	9·5	7·8
C_6H_{13}	136—137	Aq. MeOH	74·4	9·8	7·3	$C_{12}H_{19}ON$	74·6	9·8	7·25
C_7H_{15}	133—134	A	75·0	10·0	6·8	$C_{13}H_{21}ON$	75·4	10·1	6·8
C_8H_{17}	132—133	A	75·9	10·4	6·5	$C_{14}H_{23}ON$	76·0	10·4	6·3
C_8H_{17} * ...	131—132 †	MeOH	75·8	10·4	6·4				
C_9H_{19}	131—131·5	MeOH	76·4	10·3	6·0	$C_{15}H_{25}ON$	76·6	10·6	6·0
$C_{10}H_{21}$	129—130	A	77·1	10·9	5·8	$C_{16}H_{27}ON$	77·1	10·8	5·6
$C_{12}H_{25}$	125—126	MeOH	—	—	4·9	$C_{18}H_{31}ON$	78·0	11·2	5·05
$C_{14}H_{29}$	123	MeOH	78·4	11·7	4·6	$C_{20}H_{35}ON$	78·7	11·5	4·6
$C_{18}H_{37}$	119·5—120	MeOH	—	—	3·9	$C_{24}H_{43}ON$	79·8	11·9	3·9

A = ether–light petroleum (b. p. 40—60°).
* 1 : 1 : 3 : 3-Tetramethylbutyl.
† Niederl (*loc. cit.*) gives no m. p.

hydrochloric acid, water, and sodium hydrogen carbonate solution, and dried (Na_2SO_4). Removal of the solvent gave a solid which crystallised from light petroleum (b. p. 40—60°) in plates m. p. 57·5—58·5° (Found: C, 81·7; H, 11·1. Calc. for $C_{16}H_{26}O$: C, 82·0; H, 11·1%). Weitzel, Queckenstedt, Grellman, and Lautner (*Z. physiol. Chem.*, 1950, **285**, 58) give m. p. 54—55°. In the reduction of ketones of higher molecular weight, a little benzene was added to prevent the accumulation of solid in the condenser, and reduction was continued until a test portion of the product gave no red precipitate or colour with 2 : 4-dinitrophenylhydrazine.

Nitration of p-n-*Alkylphenols.*—(a) *Side chains up to* C_8. A solution of the phenol (1 g.) in glacial acetic acid (3 ml.) was stirred for 1 hr. at 5—10° during the dropwise addition of nitric acid (2 ml.; *d* 1·18). After dilution, the product was isolated with ether, and the extract washed with water and sodium hydrogen carbonate solution, and dried. The residue left after removal of the solvent was distilled *in vacuo*.

(b) *Side chains up to* C_{18}. Procedure was as in (a) except that glacial acetic acid (32 ml.) and nitric acid (4 ml.; *d* 1·18) were used and the optimum temperature was slightly higher. The

yellow crystalline product was collected, washed with water, dried, and recrystallised. Analytical details for new compounds are tabulated.

4-n-*Alkyl*-2-*aminophenols* (see Table).—A solution of the appropriate nitro-compound in the minimum amount of tetrahydrofuran required for solution was shaken in the presence of Raney nickel in hydrogen until uptake ceased. The product was isolated by removal of the solvent (after removal of the catalyst by centrifuging or filtration).

5-*Alkyl*-8-*hydroxyquinolines* (see Table).—The appropriate 4-*n*-alkyl-2-aminophenol (5 g.), concentrated sulphuric acid (10 ml.), and glycerol (5 ml.) were mixed and heated at 140—150° for 0·5 hr., then arsenic pentoxide (5 g.) was added and heating continued for a further 4 hr. The cooled mixture was diluted with water, excess of sodium carbonate added, and the crude product isolated by continuous extraction with chloroform. Evaporation of the chloroform left a dark brown viscous product which was purified by sublimation at 120°/0·5 mm., and then crystallised to constant m. p. The *hydrochlorides* were prepared by treating an ethereal solution of the base with dry hydrogen chloride and recrystallising the salt from ethyl alcohol–ether.

5-Alkyl-8-hydroxyquinolines.

			Found (%)				Required (%)			Hydrochloride		
Alkyl	M. p.	Solv.	C	H	N	Formula	C	H	N	M. p.	Found : Cl (%)	Reqd. : Cl (%)
CH_3 *	121—122°	D	—	—	8·8	$C_{10}H_9ON$	75·5	5·7	8·8	280—282°	18·1	18·1
C_2H_5	105—106	MeOH	76·3	6·4	8·0	$C_{11}H_{11}ON$	76·3	6·4	8·1	270—280 (subl.)	16·9	16·9
C_3H_7 †	57—58	D	—	—	7·5	$C_{12}H_{13}ON$	77·0	7·0	7·5	245—246	15·9	15·9
C_4H_9	55—56	D	77·5	7·5	7·0	$C_{13}H_{15}ON$	77·6	7·5	7·0	211—212	15·2	15·0
C_5H_{11}	74—75	D	77·9	7·9	6·5	$C_{14}H_{17}ON$	78·1	7·9	6·5	242—243	14·4	14·1
C_6H_{13}	60—61	D	78·2	8·3	6·1	$C_{15}H_{19}ON$	78·6	8·3	6·1	228—230	13·3	13·4
C_7H_{15}	59—60	D	78·9	8·7	5·8	$C_{16}H_{21}ON$	79·0	8·6	5·8	228—230	12·9	12·7
C_8H_{17}	59—60	D	79·0	9·0	5·6	$C_{17}H_{23}ON$	79·4	8·9	5·5	—	—	—
C_9H_{19}	62—62·5	D	79·6	9·3	5·4	$C_{18}H_{25}ON$	79·7	9·2	5·2	—	—	—
$C_{10}H_{21}$	66—67	D	79·9	9·6	5·3	$C_{19}H_{27}ON$	80·0	9·5	4·9	—	—	—
$C_{13}H_{25}$	74·5—75	MeOH	80·2	9·9	4·4	$C_{21}H_{31}ON$	80·5	9·9	4·5	—	—	—
$C_{14}H_{29}$	82—83	C	80·9	10·1	4·0	$C_{23}H_{35}ON$	80·9	10·3	4·1	—	—	—
$C_{18}H_{37}$	84·5—85·5	MeOH	81·5	10·8	3·9	$C_{27}H_{43}ON$	81·6	10·8	3·5	—	—	—

C = methyl alcohol–acetone. D = aqueous methanol.
* Noelting and Trautmann (*loc. cit.*) give m. p. 122—124°.
† Albert and Magrath (*loc. cit.*) give m. p. 60—61°.

Attempted Preparation of 8-*Hydroxy*-5-(1 : 1 : 3 : 3-*tetramethylbutyl*)*quinoline*.—(*a*) Reaction as above, gave a sublimed product which after recrystallisation from aqueous methyl alcohol had m. p. 73 –74°.

(*b*) A reaction as described by Niederl (*loc. cit.*) gave a sublimed product which after recrystallisation from aqueous methyl alcohol had m. p. 73—74° [Found (product from *a*) : C, 74·3; H, 4·7; N, 9·7; (product from *b*) C, 74·4; H, 4·8; N, 9·6. Calc. for C_9H_7ON : C, 74·5; H, 4·8; N, 9·65%]. Products from *a* and *b* both failed to depress the m. p. of 8-hydroxyquinoline.

Attempted Preparation of 5-tert.-*Butyl*-8-*hydroxyquinoline*.—The Skraup reaction with 2-amino-4-*tert*.-butylphenol was performed as described above; the sublimed product had m. p. 68—70°, raised by crystallisation from methyl alcohol to 73—74°, undepressed by 8-hydroxyquinoline (Found : C, 74·4; H, 4·8; N, 9·7%).

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