984. *Fungicidal Activity and Chemical Constitution. Part VIII.* Synthesis of 6-n-Alkyl-8-hydroxyquinolines.*

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Seven new analogues have been prepared for an investigation into the rôles played by chelation and lipoid solubility in the fungistatic activity of 8-hydroxyquinoline.

When tested as unchelated molecules against the mycelium of *Aspergillus niger*, the 5-n-alkyl-8-hydroxyquinolines prepared earlier [1] showed maximum fungistatic activity at a chain length of 5—6 carbon atoms, whereas in the presence of metal ions the pattern of fungistatic activity was markedly different.[2] Thus, maximum activity in the presence of Cu^{2+}, Fe^{2+}, Zn^{2+} was found with 8-hydroxyquinoline and the 5-methyl analogue.

Chelate compounds based on 8-hydroxy-6-methylquinoline have been mentioned as fungicides in two patents cited by Hollingshead [3] but this appears to be the only 6-n-alkyl-8-hydroxyquinoline so far described. In view of the results obtained with 5-substituted 8-hydroxyquinolines, some of the higher members of the 6-n-alkyl series have been examined.

Fischer and Willmach [4] prepared 8-hydroxy-6-methylquinoline by sulphonation of the toluene-*p*-sulphonyl derivative of *p*-toluidine, followed by a Skraup reaction and subsequent fusion with sodium hydroxide. We found this method preferable to that involving nitration of the *m*-alkylphenol, reduction, and subsequent Skraup reaction, and it was therefore used for all members of the series. In another route good yields of 6-alkyl-8-nitroquinolines were obtained by the Skraup reaction but reduction to the corresponding amines and decomposition of the derived diazonium salts [5] gave only negligible yields of the required 8-hydroxyquinolines.

* Part VII, Byrde and Woodcock, *Ann. Appl. Biol.*, 1959, **47**, 332.

[1] Woodcock, *J.*, 1955, 4391.
[2] Byrde, Clifford, and Woodcock, *Ann. Appl. Biol.*, 1958, **46**, 167.
[3] Hollingshead, "Oxine and its derivatives," Butterworths, London, 1956, p. 800.
[4] Fischer and Willmach, *Ber.*, 1884, **17**, 441.
[5] Noelting and Trautmann, *Ber.*, 1890, **23**, 3669.

Biological testing was carried out (as previously described [2]) by Dr. R. J. W. Byrde using *A. niger*, and the results will be published elsewhere later.

Experimental

n-Alkyl p-*Aminophenyl Ketones*.—Hartung and Foster's method [6] was satisfactory with the following modification. After the Fries migration, which was done in carbon disulphide, the mixture was cooled, decomposed with ice-cold 10% hydrochloric acid, and extracted with ether. Evaporation of the solvents gave an oil which was hydrolysed by refluxing it overnight with 20% hydrochloric acid. The solution was then cooled, made alkaline with 40% sodium hydroxide, and extracted with ether. Removal of solvent from the dried (Na_2SO_4) extract and distillation of the residue gave aniline followed by the required amino-ketone.

n-Alkyl p-*aminophenyl ketones.*

			Found (%)				Required (%)		
Alkyl	M. p.	Solvent †	C	H	N	Formula	C	H	N
C_3H_7	94—95° *	Aq. MeOH	73·5	8·1	8·6	$C_{10}H_{13}NO$	73·6	8·0	8·6
C_4H_9	71—72	A	74·4	8·3	7·8	$C_{11}H_{15}NO$	74·6	8·5	7·9
C_5H_{11}	95—95·5	Aq. MeOH	75·7	8·8	7·7	$C_{12}H_{17}NO$	75·4	8·9	7·3
C_6H_{13}	83—84	B	76·3	8·8	7·2	$C_{13}H_{19}NO$	76·1	9·3	6·8
C_7H_{15}	105—105·5	B	76·4	9·9	6·45	$C_{14}H_{21}NO$	76·7	9·6	6·4

* Kunckel [9] gives m. p. 84°.
† A = benzene–light petroleum (b. p. 40—60°); B = benzene–light petroleum (b. p. 60—80°);

p-*n-Alkylanilines*.—These were conveniently prepared by hydrazine reduction [7] of the above amino-ketones and were isolated by steam distillation. *p*-Ethylaniline was obtained similarly from commercially available *p*-nitroacetophenone. Attempts to prepare *p*-nitropropiophenone by Comanducci and Pescitelli's method [8] gave only benzoic acid. Analytical details for the toluenesulphonyl derivatives are given in the Table.

p-*n-Alkyl*-N-(*toluene*-p-*sulphonyl*)*anilines*.

			Found (%)				Required (%)		
Alkyl	M. p.	Solvent †	C	H	N	Formula	C	H	N
C_2H_5	90°	B	65·4	6·2	5·4	$C_{15}H_{17}NO_2S$	65·5	6·2	5·1
C_3H_7	114—114·5 *	B	66·7	6·4	4·7	$C_{16}H_{19}NO_2S$	66·4	6·6	4·8
C_4H_9	80·5—81·5	B	67·4	6·9	4·4	$C_{17}H_{21}NO_2S$	67·3	6·9	4·6
C_5H_{11}	68—68·5	C	68·0	7·2	4·4	$C_{18}H_{23}NO_2S$	68·1	7·25	4·4
C_6H_{13}	76—76·5	Aq. MeOH	68·7	7·9	4·1	$C_{19}H_{25}NO_2S$	68·9	7·6	4·2
C_7H_{15}	75—76	Aq. MeOH	69·3	7·7	4·4	$C_{20}H_{27}NO_2S$	69·6	7·8	4·1

* Hickinbottom and Waine [10] give m. p. 113—114°
† C = light petroleum (b. p. 40—60°).

4-*n-Hexylaniline*-2-*sulphonic Acid*.—The preparation of this compound is typical of the method used for the sulphonic acids listed in the Table. The toluene-*p*-sulphonyl derivative of *p*-n-hexylaniline (5 g.), sulphuric acid (6 ml.), and oleum (2 ml.) were heated at 96° for 2 hr., and the mixture poured on crushed ice (50 g.). The product was collected, washed with water, and crystallised from aqueous ethyl alcohol (3·2 g., 44%).

4-*n-Alkylaniline*-2-*sulphonic acids.*

			Found (%)					Required (%)			
Alkyl	M. p.	Solvent	C	H	N	S	Formula	C	H	N	S
C_2H_5	>300°	H_2O	47·9	5·6	6·7	15·75	$C_8H_{11}NO_3S$	47·8	5·5	7·0	15·95
C_3H_7	>300	H_2O	—	—	6·6	14·8	$C_9H_{13}NO_3S$	50·2	6·0	6·5	14·9
C_4H_9	265—266 (decomp.)	MeOH	52·4	7·0	6·0	13·7	$C_{10}H_{15}NO_3S$	52·4	6·6	6·1	14·0
C_5H_{11}	267—268 (decomp.)	MeOH	54·6	7·1	5·9	13·4	$C_{11}H_{17}NO_3S$	54·3	7·0	5·8	13·2
C_6H_{13}	263—264 (decomp.)	Aq. MeOH	55·7	7·3	5·2	12·25	$C_{12}H_{19}NO_3S$	56·0	7·4	5·4	12·5
C_7H_{15}	263—264 (decomp.)	Aq. EtOH	—	—	5·5	12·1	$C_{13}H_{21}NO_3S$	57·5	7·75	5·2	11·8
C_8H_{17}	265—266 (decomp.)	MeOH	58·6	7·7	5·2	11·3	$C_{14}H_{23}NO_3S$	59·0	8·1	4·9	11·25

[6] Hartung and Foster, *J. Amer. Pharm. Assoc.*, 1946, **35**, 15.
[7] Huang-Minlon, *J. Amer. Chem. Soc.*, 1948, **70**, 2803.
[8] Comanducci and Pescitelli, *Gazzetta*, 1906, **36**, 790.
[9] Kunckel, *Ber.*, 1900, **33**, 2643.
[10] Hickinbottom and Waine, *J.*, 1930, 1558.

6-*n-Propylquinoline*-8-*sulphonic Acid.*—Typical details of the preparation of the 6-n-alkylquinoline-8-sulphonic acids, based on those of Richter and Smith,[11] are given below. A mixture of 4-n-propylaniline-2-sulphonic acid (3·6 g.), dried glycerol (5·5 g.), ferrous sulphate (2 g.), and sulphuric acid (8 ml.) was stirred and heated at 80—100° for 0·5 hr. After addition of arsenic pentoxide (3 g.) heating was continued at 130—140° until the mixture solidified (1—2 hr.); it was then extracted with boiling water (3 × 50 ml.), and the extracts were combined, filtered, and cooled. The product crystallised in fine needles (2·6 g., 62%).

With homologues from hexyl upwards the solid mixture was triturated with cold water and filtered and the residue extracted (Bolton extractor) with ethyl alcohol for 2—3 hr.

Since these acids were troublesome to burn and gave unreliable carbon values, only nitrogen (Dumas) and sulphur (Schöniger) [12] values are given in the Table.

6-*n-Alkylquinoline*-8-*sulphonic acids.*

Alkyl	M. p.	Solvent	Found (%) N	Found (%) S	Formula	Required (%) N	Required (%) S
C_2H_5	>300°	H_2O	5·7	13·5	$C_{11}H_{11}NO_3S$	5·9	13·5
C_3H_7	>300	H_2O	5·35	12·2	$C_{12}H_{13}NO_3S$	5·6	12·8
C_4H_9	273—274	H_2O	5·0	12·2	$C_{13}H_{15}NO_3S$	5·3	12·1
C_5H_{11}	297—298	Aq. EtOH	5·3	11·2	$C_{14}H_{17}NO_3S$	5·0	11·5
C_6H_{13}	266—267	MeOH	4·9	10·7	$C_{15}H_{19}NO_3S$	4·8	10·9
C_7H_{15}	262—263	Aq. EtOH	4·7	10·4	$C_{16}H_{21}NO_3S$	4·6	10·4
C_8H_{17}	234·5—235·5	MeOH	4·6	9·9	$C_{17}H_{23}NO_3S$	4·4	10·0

6-*n-Heptyl*-8-*hydroxyquinoline.*—6-n-Heptylquinoline-8-sulphonic acid (0·5 g.) was stirred with molten potassium hydroxide (2·5 g.) for 2—3 min. The cooled melt was then lixiviated with water, acidified with hydrochloric acid, and basified with ammonia solution (*d* 0·88). The product, isolated by steam distillation and ether extraction of the distillate, crystallised from light petroleum (b. p. 40—60°); it (0·3 g.) had m. p. 64—65°.

The lower homologues were readily purified by sublimation *in vacuo*.

6-*n-Alkyl*-8-*hydroxyquinolines.*

Alkyl	M. p.	Solvent	Found (%) C	Found (%) H	Found (%) N	Formula	Required (%) C	Required (%) H	Required (%) N
C_2H_5	75·5—76·5°	Aq. MeOH	76·0	6·3	8·0	$C_{11}H_{11}NO$	76·3	6·4	8·1
C_3H_7	51·5—52·5	A	77·0	7·2	7·5	$C_{12}H_{13}NO$	77·0	6·95	7·4
C_4H_9	70—71	Aq. MeOH	77·8	7·8	6·8	$C_{13}H_{15}NO$	77·6	7·5	7·0
C_5H_{11}	35—36	A	78·0	8·2	6·4	$C_{14}H_{17}NO$	78·1	7·9	6·5
C_6H_{13}	65—65·5	B	78·4	8·5	5·9	$C_{15}H_{19}NO$	78·6	8·3	6·1
C_7H_{15}	64—65	C	79·2	8·7	6·0	$C_{16}H_{21}NO$	79·0	8·6	5·8
C_8H_{17}	53·5—54·5	B	78·9	8·7	5·5	$C_{17}H_{23}NO$	79·4	8·95	5·45

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[11] Richter and Smith, *J. Amer. Chem. Soc.*, 1944, **66**, 396.
[12] Schöniger, *Mikrochim. Acta*, 1956, 869.