[Jour. Indian Chem. Soc., Vol. 42, No. 6, 1965]

Synthesis of Possible Antiamoebic Agents. Part III

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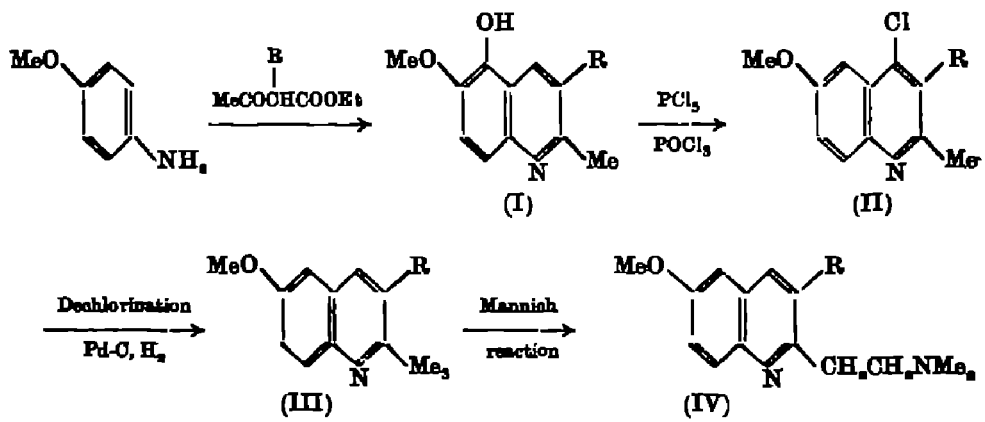
2-β-Dimethylaminoethyl-3-alkyl-6-methoxyquinolines with alkyl groups (n-Bu, isoamyl, and n-hexyl) have been synthesised with a view to testing their amoebacidal activity.

In continuation of our previous work[1] the synthesis of 2-β-dimethylaminoethyl-3-alkyl-6-methoxyquinoline having alkyl groups as n-butyl, isoamyl, and n-hexyl is described herein. The reaction takes place along the following route.



Alkyl acetoacetic esters were prepared according to Vogel[2]. 2-Methyl-3-alkyl-4-hydroxy-6-methoxyquinolines (I) were synthesised in very good yields, following the Conard-Limpach reaction[3]. These were converted to substituted 4-chloroquinolines (II) by heating in an oil bath at 125° for 3 hr. with a mixture of $POCl_3$ and PCl_5 according to the method of Pathak and Pathak[4]. In the case of isoamyl and n-hexyl, the yield was reduced to 30% and 25%, respectively. On heating with $POCl_3$ and PCl_5 separately, resinous mass was formed. Similarly, raising the heating period even to 24 hr. with a mixture of $POCl_3$ and PCl_5 formed the resinous mass. From these resinous products the required chloro compounds were obtained in poor yields. The dechlorination of (II) was achieved by hydrogenation under pressure in presence of Pd-C catalyst to form the compounds of type (III), which on subjecting to the Mannich reaction yielded the desired 2-β-dimethylaminoethyl-3-alkyl-6-methoxyquinolines (IV) in moderate yields.

1. This issue, p. 403.
2. Vogel, "Elementary Practical Organic Chemistry", 1957, Part I, p. 212.
3. *J. Chem. Soc.*, 1947, 1034.
4. This *Journal*, 1960, **37**, 282.

TABLE I

R.	%Yield.	M.P. or B.P.	Picrate M.P.	Formula.	%Carbon. Found.	%Carbon. Reqd.	%Hydrogen. Found.	%Hydrogen. Reqd.	%Nitrogen. Found.	%Nitrogen. Reqd.	%OMe. Found.	%OMe. Reqd.	%Chlorine. Found.	%Chlorine. Reqd.
2-Methyl-3-alkyl-4-hydroxy-6-methoxyquinoline (I).														
n-Bu	81.6	247°	190°	$C_{15}H_{19}O_2N$	73.10	73.46	7.55	7.75	5.50	50.71	12.35	12.65	13.1	13.4
Isoamyl	73.3	226°	156°	$C_{16}H_{21}O_2N$	74.00	74.13	7.91	8.10	5.12	5.40	11.70	11.93		
n-Hexyl	65.9	206°	240°	$C_{17}H_{23}O_2N$	74.52	74.72	8.13	8.42	4.90	5.12	11.15	11.35		
2-Methyl-3-alkyl-4-chloro-6-methoxyquinoline (II).														
n-Bu	74.5	66°	196°	$C_{15}H_{18}ONCl$	68.10	68.31	6.80	6.81	5.10	5.30	11.40	11.70	13.1	13.4
Isoamyl	31.2	65°	162°	$C_{16}H_{20}ONCl$	68.90	69.18	7.00	7.20	4.80	5.00	10.90	11.10	12.5	12.7
n-Hexyl	25.0	305°(d)	196°	$C_{17}H_{22}ONCl$	69.62	69.98	7.32	7.54	4.60	4.80	10.40	10.60	11.9	12.1
2-Methyl-2-alkyl-6-methoxyquinoline (III).														
n-Bu	75.0	160°/1mm	205°	$C_{15}H_{19}ON$	78.32	78.60	7.93	8.29	5.90	6.10	13.20	13.50		
Isoamyl	57.6	180°/1	174°	$C_{16}H_{21}ON$	78.85	79.01	8.35	8.64	5.50	5.70	12.50	12.70		
n-Hexyl	66.6	190°/1	170°	$C_{17}H_{23}ON$	79.01	79.37	8.88	8.95	5.10	5.40	11.80	12.00		
2-β-Dimethyl-aminoethyl-3-alkyl-6-methoxyquinoline (IV).														
				Picrates.										
n-Bu	47.0	..	170°	$C_{24}H_{29}O_8N_5$	55.80	55.92	5.33	5.63	13.30	13.50	5.70	6.00		
Isoamyl	41.1	..	145°	$C_{25}H_{31}O_8N_5$	56.40	56.71	5.60	5.86	13.10	13.20	5.50	5.80		
n-Hexyl	44.4	..	98°	$C_{26}H_{33}O_8N_5$	57.31	57.46	5.82	6.08	12.60	12.80	5.40	5.70		

EXPERIMENTAL

2-Methyl-3-alkyl-4-hydroxy-6 methoxyquinoline (I : R = *n*-Bu, isoamyl, *n*-hexyl).—A mixture of *p*-anisidine (0.1*M*), 2-*n*-alkyl acetoacetic ester (0.11*M*), 3-4 drops of HCl (conc.), and benzene (*ca.* 50 ml) after keeping overnight was heated in an oil bath at 120-30° in a Dean-Stark apparatus till no more water had collected; benzene was then distilled, the residual viscous mass kept overnight, and then poured on boiling diphenyl oxide (*ca.* 200 ml). After boiling for 15 to 20 min, the mass was cooled and diluted with petroleum (b.p. 60-80°). It was then kept overnight, filtered, and washed with light petroleum. It was crystallised from ethanol.

2-Methyl-3-alkyl-4-chloro-6-methoxyquinoline (II: R = *n*-Bu, isoamyl, *n*-hexyl).—A mixture of the preceding quinoline (I, 15 g.), PCl_5 (0.01*M*, 3 g.), and $POCl_3$ (35 ml, 0.2*M*) was heated in an oil bath with a bulb condenser, fitted with a guard tube, at 120-25° for 3 hr. The product was cooled and poured on crushed ice. The aqueous solution was neutralised with liquor ammonia under cooling till distinctly alkaline. The separated solid mass was filtered and dissolved in HCl (dil.). The impurities (resins) were removed by extracting with benzene. The acidic layer was clarified by animal charcoal, filtered, and basified with liquor ammonia under cooling. The chloro compound separted as a white crystalline mass. It was recrystallised from ethanol in white needles.

2-Methyl-3-alkyl-6-methoxyquinoline (III: R = *n*-Bu, isoamyl, *n*-hexyl).—A mixture of quinoline (II, 0.009*M*), anhydrous sodium acetate (0.01*M*, 1.02 g.), glacial acetic acid (20 ml), anhydrous ethanol (30 ml), and palladium charcoal (0.5 g.) as a catalyst was kept in the reduction chamber of the hydrogenation plant. and worked up as described in Part II[1] in the case of 2-methyl-3-alkyl-6-methoxyquinoline (III). When the filtrate was neutrallised with KOH solution under cooling, an oil separated, which was extracted with benzene. The benzene extract was washed with water and dried over anhydrous sodium sulphate. After removal of the benzene the residual oil was distilled under reduced pressure.

2-β-Dimethylaminoethyl-3-alkyl-6-methoxyquinoline (IV : R = *n*-butyl, isoamyl, *n*-hexyl).—A mixture of the preceding quinoline (III, 0.006*M*), paraformaldehyde (0.01*M*, 0.55 g.), and dimethylamine hydrochloride (0.06*M*, 0.55g.), was worked up as described in Part II in the case of 2-β-dimethyl-3-alkyl-6-methoxyquinoline (IV). The base was obtained as a viscous mass.

The *picrate*, prepared in usual manner, was crystallised from anhydrous ethanol.

The authors express their sincere thanks to Dr. Shiv Mangal Singh 'Suman', Principal, Madhav College, Ujjain, for providing research facilities and to Dr. C. N. Kachru, Reader, Department of Chemistry, University of Jammu & Kashmir, for his keen interest during the course of the investigation.

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Received September 11, 1964.