J. Indian Chem. Soc.,
Vol. LIII, October 1976, pp. 1038-1040

Synthesis of Possible Antiamebic Agents

R. MUKHOPADHYAY and B. PATHAK*

Department of Applied Chemistry, Calcutta University

92, Acharya Prafulla Chandra Road, Calcutta-700 009.

Manuscript received 27 June 1974 ; revised 9 April 1976 ; accepted 30 June 1976

Synthesis of some halohydroxyquinolines, examination of their antiamebic activity and studies on halogenation of 8-hydroxyquinolines with iodine trichloride and iodine monochloride have been carried out.

5-Chloro-7-iodo-8-hydroxyquinoline and 5, 7-diiodo-8-hydroxyquinoline are potent oral antiamebic agents known over the past three decades. A large number of halohydroxyquinolines[1-4] iodinated and noniodinated were prepared after the discovery of these two drugs ; some of them are highly effective against *E. histolytica*.

One of the compounds viz. (2-diethylaminoethyl-3-n-propyl-4-chloro-5 or 7-iodo-8-hydroxyquinoline) synthesized by Pathak and Pathak[5] showed *in vitro* activity[6] about tenfold that of 5-chloro-6-iodo-8-hydroxyquinoline. High activity might be due to extra chelation centre in the compound. The present authors have prepared compounds of a similar type and a few halohydroxyquinaldines of the general formula (I) (Fig. 1) with an object to find out, if possible, a more potent oral drug than the existing halohydroxyquinolines.

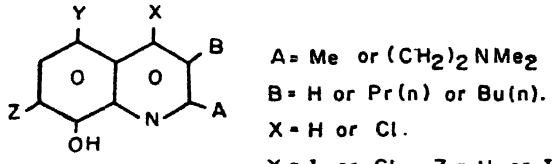

FIG. 1

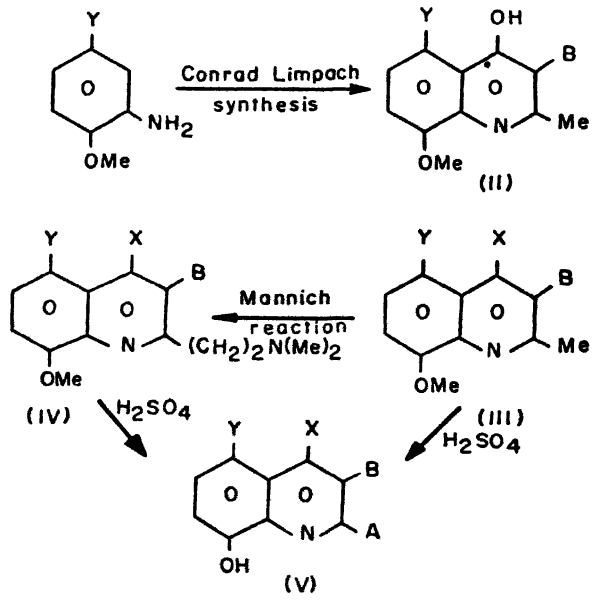

FIG. 2

Halogenation of 8-hydroxyquinolines was effected by using ICl_3 as well as ICl. It is known that 8-hydroxyquinoline, on halogenation with ICl_3 yields 5-chloro-7-iodo derivative[7,8]. Interaction of ICl_3 with 8-hydroxyquinolines substituted at 3 and 4-positions, reported in this paper has also yielded 5-chloro-7-iodo compounds. The orientation has been established in the scheme shown in Fig. 3.

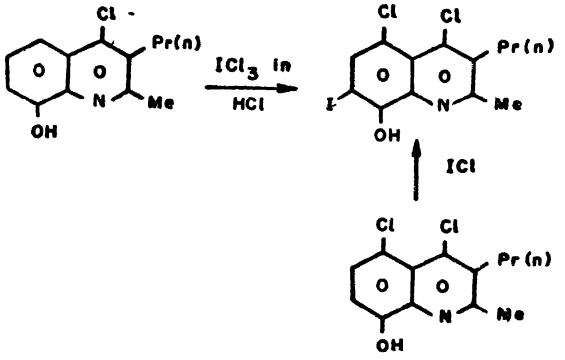

Fig. 3.

Thus it appears that on halogenation of 8-hydroxyquinoline compounds with ICl_3, iodine chooses to enter at the 7-position preferentially.

Iodination of 8-hydroxyquinolines has also been studied using ICl. It has been observed that when ICl in HCl (15%) is used for iodination of 3 and 4-substituted 8-hydroxyquinoliness in HCl (15%) the resultant product is a monoiodo compound. If, however, ICl is used in glacial AcOH medium, formation of a diiodo compound occurs.

*Senior author

TABLE

C_9H_2 ONABXYZ (I)

No.	Method	A	B	X	Y	Z	m.p.°	Picrate m.p.°	Found %	Calc. for	Per cent	In vitroamoebacidal Conc. mcg./ml.
1.	—	Me	Pr	H	H	H	45[e]	—	N, 6.72	$C_{13}H_{15}ON$	N, 6.965	—
2.	—	$(CH_2)_2N(Me)_2$	Pr	H	H	H	—	189[f]	N, 14.07	$C_{22}H_{25}O_8N_5$	N, 14.37	—
3.	—	Me	Pr	Cl	Cl	H	89[f]	—	N, 5.01	$C_{13}H_{13}ONCl_2$	N, 5.184	—
4.	—	Me	Bu	Cl	H	H	—	179[g]	N, 11.5	$C_{20}H_{19}O_8N_4Cl$	N, 11.7	—
5.	(a)	Me	H	Cl	Cl	I	125	—	I, 35.7	$C_{10}H_6ONCl_2I$	I, 35.8	1000
6.	(a)	Me	Pr	Cl	Cl	I	148	—	I, 31.8	$C_{13}H_{12}ONCi_2I$	I, 32.1	Not active
7.	(a)	Me	Pr	H	Cl	I	110	—	I, 34.8	$C_{18}H_{13}ONClI$	I, 35.1	Not active
8.	(a)	$(CH_2)_nNMe_2$	Pr	H	Cl	I	180-5 (d)	—	I, 29.9	$C_{16}H_{20}ON_2ClI$	I, 30.3	31.25
9.	(b)	Me	H	Cl	I	H	107	—	I, 40.2	$C_{10}H_7ONClI$	I, 39.87	125
10.	(b)	Me	Pr	Cl	I	H	114	—	I, 35.4	$C_{13}H_{13}ONClI$	I, 35.14	Not active
11.	(b)	Me	Bu	Cl	I	H	99	—	I, 33.3	$C_{14}H_{15}ONClI$	I, 33.88	Not active
12.	(b)	$(CH_2)_2NMe_2$	Pr	H	I	H	125-30 (d)	—	I, 32.6	$C_{16}H_{21}ON_2I$	I, 33.07	Not active
13.	(b)	$(CH_2)_2NMe_2$	Pr	Cl	I	H	160-70 (d)	—	I, 30.0	$C_{16}H_{20}ON_2ClI$	I. 30.35	62.5
14.	(a)	$(CH_2)_2NMe_2$	Pr	Cl	Cl	I	decomp>160	—	I, 27.6	$C_{16}H_{19}ON_2Cl_2I$	I, 28.03	62.5
15.	(c)	Me	H	Cl	I	I	156-8	—	I, 56.8	$C_{10}H_6ONClI_2$	I, 57.0	250
16.	(c)	Me	Pr	H	I	I	131	—	I, 55.7	$C_{13}H_{13}ONI_2$	I, 56.1	250
			Eemetine									10
			Iodochlorohydroxyquinoline									100

d) With decomposition. e) Recrystallised from dil. alcohol. f) Recrystallised from alcohol. g) Recrystallised from toluene.
All the compound from No. 5 to No. 16 were recrystallised from alcohol except No. 15 which was recrystallised from gl. AcOH.

The monoiodo compounds are probably 5-iodo compounds. Das and Mukherjee[8] had shown that interaction of 8-hydroxyquinoline with ICl in HCl medium yielded 5-iodo-8-hydroxyquinoline HCl.ICl addition compound, which on stirring with water produced 5, 7-diiodo compound. Monoiodo compounds reported in this paper, however, escape further iodination.

Pharmacology :

The halohydroxyquinolines thus synthesized were examined for their antiamebic activity, as shown in the table.

Experimental

2-Methyl 3-n-propyl 8-methoxyquinoline : (III ; B=Pr(n) ; X = Y=H)

2-Methyl-3-n-propyl-4-chloro -8- methoxyquinoline[5] was dehalogenated by hydrogenation in the presence of pd/C[4]. The product was recrystallised from pet. ether (60°—80°)-m.p. 60°. Picrate recrystallised from alcohol, m. p. 160° – 62°. (Found : C, 77.9% ; H, 7.8% Calc. for $C_{14}H_{17}ON$: C, 78.14% ; H, 7.907%).

2-(2-Dimethylaminoethyl)-3-n-propyl - 8 -methoxyquinoline : (IV ; B = Pr(n) ; X=Y = H) : It was prepared by the Mannich reaction of III (B = C_3H_7 (n) ; X=Y = H[10]. Picrate recrystallised from alcohol, m.p. 148°. Found, N, 13.4%, Calc. for $C_{23}H_{27}O_8N_5$; N, 13.97%.

2-Methyl-3-n-propyl-4-hydroxy-5-chloro-8-methoxyquinoline (II ; B = Pr(n) ; Y=Cl) : It was prepared by the Conrad Limpach synthesis using 2-amino-4-chloroanisole and propylacetoacetic ester[5]. The product was recrystallised from alcohol, m. p. 224° (Found : C, 63.2% ; H, 5.93% N, 5.07%. Calc. for $C_{14}H_{16}O_2NCl$; C, 63.28% ; H, 6.027% ; N, 5.28%).

2-Methyl 3-n-propyl-4, 5-dichloro-8-methoxyquinoline : (III ; B=Pr(n) ; X=Y = Cl) (II ;B = Pr(n), Y = Cl) was heated with a mixture of $POCl_3$ and PCl_5 and worked out as usual[5]. It was recrystallised from dil. alcohol, m. p. 116°-18° (Found : N, 4.81% ; Cl 24.7%. Calc. for $C_{14}H_{15}ONCl_2$: N, 4.92% ; Cl, 25.00%).

Demethylation of 8-methoxyquinolines : 8-Methoxy compounds were demethylated by refluxing with H_2SO_4 (70%) and in some cases with HBr (48%)[10]. Data of the 8-hydroxyquinolines prepared are listed in the table.

Halogenation of 8-hydroxyquinolines(V) :

(a) To a solution of ICl_3 (20%, 0.015 mol) in conc. HCl, was added dropwise a solution of the appropriate 8-hydroxyquinoline (0.01 mol) in conc. HCl or dil. HCl (15%) with stirring. The reaction product was worked out as usual[8].

(b) Method adopted by Viktor Papesch and Robert R. Burtner[9] was followed.

(c) A solution of appropriate 8-hydroxyquinoline (0.01 mol) in gl. AcOH was added to a solution of ICl (0.04 mol) in gl. AcOH. The mixture was allowed to stand for 30 hr. and was added dropwise to dil. HCl (15%) with stirring when the product precipitated out. It was worked out in the usual manner[8,9]. Data of the compounds prepared are listed in the table.

Determination of orientation of iodine and chlorine during interaction of substituted 8-hydroxyquinolines and iodine trichloride : A solution of V (A=Me ; B=Pr (n) ; X=Y = Cl) was iodinated by the method (c) stated above.

The product was recrystallised from alcohol, m. p. of the compound obtained by interaction of ICl_3 and V (A=Me ; B=Pr (n) ; X = Cl ; Y=H) was also 148°. Ir spectra of both the compounds were identical.

Acknowledgement

The authors are grateful to the CSIR, India for the award of a fellowship to one of the authors (RM) and to CDRI, India for providing with antiamebic screening report.

References

1. Alfred Burger, Medicinal Chemistry, 3rd. Ed. Part I. 1969, p. 540.
2. Ruetgerswerke and Teerverwertung, A. G. Fr. 1, 549, 819 (Cl. CO7D) 13 Dec., 1968.
3. A. F. Helin and C. A. Vander Werf, *J. Org. Chem.*, 1952, 17, 229.
4. R. Gopalchari, *J. Sci. Ind. Res., (India)*, 1960, **19C**, 296.
5. K. L. Pathak and B. Pathak, *J. Indian Chem. Soc.*, 1960, 37, 231.
6. Private Communication.
7. S. L. Mukherjee, 1946 Indian Pat. 34380.
8. A. Das and S. L. Mukherjee *J. Org. Chem.*, 1957, **22**, 1111.
9. V. Papesch and R. R. Burther, *J. Amer. Chem. Soc.*, 1936, **58**, 1314.
10. R. Mukhopadhyay, D. Ghosh and B. Pathak, *J. Indian Chem. Soc.*, 1974, **51**, 880.