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SYNTHESIS OF CERTAIN 8-[2-HYDROXY-3-(SUBSTITUTEDAMINO) PROPOXY]QUINOLINES AS B-ADRENERGIC BLOCKING AGENTS*

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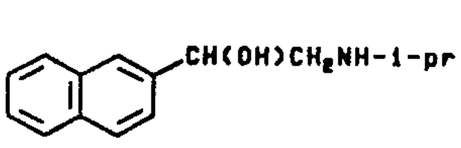
ABSTRACT

The reaction of 8-hydroxyquinoline I with epichlorohydrin in the presence of potassium carbonate yielded a mixture of the epoxide II and the chlorohydrin III. The reaction of certain amines with a mixture of II and III afforded 8-[2-hydroxy-3-(substitutedamino) propoxy] quinoline Iva-h. The structure of the synthesized compounds was established by microanalyses and ^{1}H-NMR spectra. The hydrolytic rate constants in aqueous solution at pH 7 and pH 12 were determined using HPLC technique.

INTRODUCTION

In the course of synthetic program on ß-adrenergic blocking agents, analogues of pronethalol(1) and propanolol(2) have been extensively studied[1].



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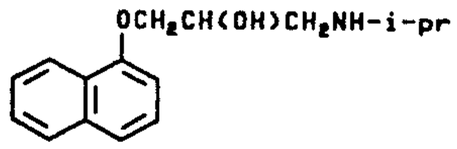

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An ethanolamine side chain or more frequently an oxypropanolamine linked to an aromatic ring are the chemical features required for ß-blocking activity[2]. However the alteration of these features does not abolish the activity, but can lead in some cases to potent ß-antagonists[3]. Also it was shown that an amidic moiety in the side chain of an arylethanolamine or an (aryloxy) propanolamine confers a high degree of cardioselectivity and ß-adrenergic blocking potency[4,5]. In addition, the cardioselectivity has also been achieved by replacing the isopropyl or tert-butyl substituent conventionally used in ß-blockers with an (aryloxy) alkyl group in which the aryl ring has a paraamidic substituent[6].

In the preceeding papers[7,8] several (aryloxy) propanolamines with an ester function incorporated into the nitrogen substituent or placed on the aryl portion of typical ß-blockers nuclei were prepared and tested as ß-adrenergic receptor blocking agents.

In our previous work the synthesis and the hydrolytic stabilities of certain new compounds where esters have been placed on the aryl portion of typical ß-blockers nuclei have been described[9,10]. With this rationale and literature precedent, the synthesis and hydrolytic stabilities of certain new compounds of 8-[2-hydroxy-3-(substitutedamino) propoxy] quinolines have been achieved.

The synthesis of compounds (IV_a-h) proceeded according to Scheme 1. The reaction of 8-hydroxyquinoline

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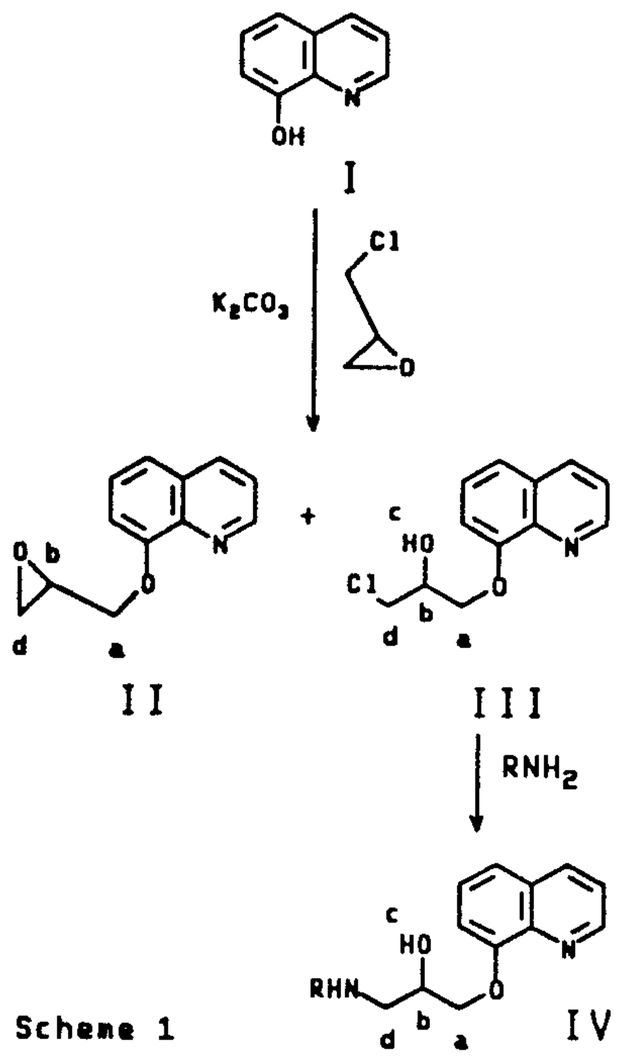
(I) with epichlorohydrin in the presence of potassium carbonate; the epoxide (II) and chlorohydrin (III) were obtained. II And III were used without further purification in most cases for the synthesis of the free amine bases (IV) by opening the epoxide through the reaction with the appropriate amines. Assignment of the chemical structure of the newly synthesized compounds IV was confirmed using microanalyses and ^{1}H-NMR spectra.



Scheme 1

EXPERIMENTAL

Chemistry :

The time required for completion of the reaction was monitored by thin layer chromatography (TLC). Melting points were determined in open glass capillaries and are uncorrected. ^{1}H-NMR spectra were measured in chloroform-d6 using TMS as internal standard on EM 360 MHz NMR spectrophotometer. Microanalyses were determined on a Perkin Elmer 240 C microanalyser at the Faculty of Seience, Assiut University.

Reaction of 8-Hydroxyquinoline with Epichlorohydrin

A mixture of 8-hydroxyquinoline (14.5 g, 0.1 mole), epichlorohydrin (50 ml) and anhydrous potassium carbonate (13.8 g 0.1 mole) in 100 ml dry acetone was stirred and heated under reflux for 2hrs. The solvent was removed under reduced pressure, the residue was poured on water (100 ml), and extracted with chloroform. The extract was washed with water (100 ml), 10% sodium hydroxide (100 ml) and water (100 ml). The extract was dried over anhydrous magnesium sulfate, filtered and removed under reduced pressure to afford a clear oil which was used without further purification for the synthesis of the free amine base (IV). The ^{1}H-NMR revealed that the oil is a mixture of the epoxide (II) and the chlorohydrin (III).

Preparation of 8-[2-Hydroxy-3-(substitutedamino)Propoxy]-quinoline IVa-h;General Procedure :

A solution of the mixture II and III (0.05 mole) in acetonitrile (80 ml) and excess of the appropriate primary amine (0.23 mole) was refluxed for 24 hr. The excess amine was removed under vacuum and the residue was allowed to solidify in the refrigerator (Table I).

RESULTS AND DISCUSSION

^{1}H-NMR ($CDCl_3$/TMS, ppm) for the epoxide II and chlorohydrin III mixture showed a peak at, δ 8.7 (m, 2H) attributed to the protons on C_2 of both II and III; 7.9-8.1 (m, 2H) assigned for protons on C_7 of II and III, 7.5 (m, 2H) attributed to the protons on C_4 of II and III and 7-7.3 (m, 6H) for protons on C_3, C_5 and C_6 in II and III.

The ^{1}H-NMR of the aliphatic residue attached to the oxygen on C_8

of quinoline moiety in II and III showed the following signals[11] : 4.2 (S, 1H) appeared to the proton of oH group in chlorohydrin III, 3.6-3.8 (m, 2H) assigned for protons on C_b for II and III, 2.3-2.5 (m, 4H) for protons of C_a of II and III, 1.2-1.6 (d, 2H) for the protons on C_d of the epoxide and 0.7-1.0 (d, 2H) for the protons of C_d of the chlorohydrin III.

Identity of the final products were confirmed by NMR spetroscopy[11] and the protons count for IVb, IVd and IVg match that of the structures. Compound IVb ^{1}H-NMR ($CDCl_3$, TMS, ppm) 8.7 (d, 1H, C_2-H), 8.2 (d, 1H, C_7-H) 7.2-7.5 (m, 4H, C_3, C_4, C_5 and C_6- protons), 5.4 (S, 1H, O-H), 4.2 (m, 1H, C_b-H), 3.4 (d,2H, C_a-H), 3-3.2 (m, 2H, C_d-H), 1.8-2.0 (m, 2H, CH_2 adjacent to N), 1.4-1.7 (m, 2H, CH_2 adjacent to CH_3), 0.9-1.2 (m, 3H, CH_3) and 0.5 (s, 1H, NH).

Similarly IVd showed 8.7 (d, 1H, C_2-H), 8.2 (d, 1H, C_7-H), 7.0-7.4 (m, 4H, C_3-H, C_4-H, C_5-H and C_6-H of quinoline moiety), 6.7-6.9 (m, 5H of phenyl residue), 4.6 (s, 1H, OH), 4.2 (m, 1H, C_b-H), 2.7 (d,2H, C_a-H), 2.1 (d, 2H, C_d-H) and 0.7 (s, 1H, NH). Also IV g showed 9.0 (d, 1H, C_2-H), 8.4 (d, 1H, C_7-H), 7.2-7.6 (m, 4H, C_3-H, C_4-H, C_5-H and C_6-H of quinoline moiety), 5.4 (s, 1H, OH) 4.2 (m, 1H, C_b-H), 2.5 (d, 2H, C_a-H), 2.3 (d, 2H, C_d-H), 1.3-1.7 (m, 4H, adjacent to N in piperidine moiety), 0.9-1.1 (m, 6H of piperidine moiety) and 0.5 (s, 1H, NH)[11].

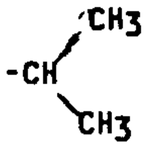
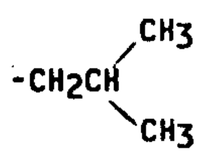
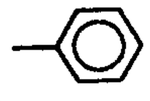
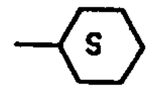
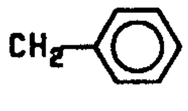
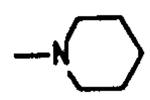
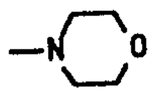
Kinetic Studies :

A high performance liquid chromatographic determination of the hydrolytic rate constants was performed, in a system of Waters Associates Model 501, WISP injector Model 710, and Model 484 absorbance detector adjusted at 254 nm. C-18 column (VYDAC, Reverse Phase, USA) was used for all separation of the newly synthesized compounds. The mobile phase which was used for the separation of all the esters and its degradation products was composed of methanol : H_2O : triethanolamine (800 : 100 : 100).

All reactions were run under-pseudo first order condition, sample of 20 ul was injected into the column at various time intervals and the hydrolytic rate constants were determined from the disappearance of the compound by linear regression of natural logarithm of peak height versus time plots.

Table II showed the observed first order hydrolytic rate constants (K) and half lives ($t_{½}$) of the eight synthesized compounds. The hydrolytic rate constants were determined, by adding a fresh concentrated solution of the free amine base in methanol to the hydrolytic medium previously equilibrated to the 37°C and mixed thoroughly to result in an initial concentration of 3 X 10^{-5}M/L. In 0.01 M phosphate buffer at pH 7.0, 37°C and at flow rate 1.5 ml min^{-1} the half-lives for all the compounds were between 2-3 days. At pH 12.0 the retention times for the synthesized compounds were between 5-30 minutes. The isopropyl (IV_a) and cyclohexyl (IV_e) derivatives hydrolysed faster than all the other compounds. Also similar pattern have been achieved with n-propyl (IV_b) and isobutyl derivatives. (IV_c). The benzyl and morpholino derivatives hydrolysed less than all the other compounds and showed certain stability in basic condition.

Table I : Melting points yield % and the microanalyses of the newly synthesized compounds (IVa-h).

Compound	R	MP°C	Yield% (solvent of cryst.)	Molecular formula	Analysis % calcd/found C	H	N
IVa		59-61	60.2(a)	$C_{15}H_{20}N_2O_2$	69.23	7.69	10.77
				(260)	68.9	7.3	10.5
IVb	$-CH_2CH_2CH_3$	62-63	59.7(b)	$C_{15}H_{20}N_2O_2$	69.23	7.69	10.77
				(260)	69.1	7.7	11.2
IVc		40-42	34.8(a)	$C_{16}H_{22}N_2O_2$	70.07	8.03	10.22
				(274)	70.5	8.3	10.7
IVd		69-71	42.2(b)	$C_{18}H_{18}N_2O_2$	73.47	6.12	9.52
				(294)	74.0	6.6	10.0
IVe		50-52	56.2(b)	$C_{18}H_{24}N_2O_2$	72.00	8.00	9.33
				(300)	71.8	7.6	9.2
IVf		70-72	70.0(a)	$C_{19}H_{20}N_2O_2$	74.03	6.49	9.09
				(308)	74.6	6.2	8.7
IVg		80-82	50.2(c)	$C_{17}H_{23}N_3O_2$	67.77	7.64	13.95
				(301)	68.1	8.1	13.5
IVh		95-97	32.0(c)	$C_{16}H_{21}N_3O_3$	63.37	6.93	13.86
				(303)	62.9	7.2	14.1

(a) = n-hexane
(b) = petroleum ether (60-50°C)
(c) = methanol-ether

Table II : The Observed Psuedo Firsr Order Hydrolytic Rate Constant (K) Half-Lives ($t_{½}$) in pH 12 ionic strength 0.05.

Compound	K (min^{-1})	$t_{½}$(min)
IVa	0.1333±0.02	5.2
IVb	0.0797±0.05	8.7
IVc	0.0648±0.01	10.7
IVd	0.0343±0.12	20.2
IVe	0.1195±0.20	5.8
IVf	0.0229±0.07	30.3
IVg	0.0441±0.03	15.7
IVh	0.0304±0.13	22.0

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تخليق بعض مشتقات ٨-(٢-هيدروكسى) ٣-ايزوبروبيل امينوبروبوكس) كينولين ذات الفاعليه البيولوجيه المتوقعة

عبـــد الحميـــد نجـيب

قسم الكيمياءالعضوية الصيدلية - كلية الصيدلة - جامعة اسيوط - اسيوط - مصر

فى هذا البحث تم تخليق عدد ثمانية استرات صيدلية جديدة من مشتقات ٨-(٢-هيدروكسى) ٣-ايزوبروبيل امينوبروبوكس) كينولين وكذلك تم تعيين ثوابت سرعة التحليل لهذه المركبات الصيدلية فى الوسط المائى.

وقد تم اثبات صحة هذه المركبات عن طريق التحليل الدقيق للعناصر وكذلك باستخدام الرنين النووى المغناطسيى. وقد تم الاستعانة بكروماتوجرافيا السوائل تحت الضغط العالى لتحليل تلك المركبات فى الوسط المائى.

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