SYNTHESIS OF SOME BENZHYDRYL DERIVATIVES OF PIPERAZINYL PROPANOLS

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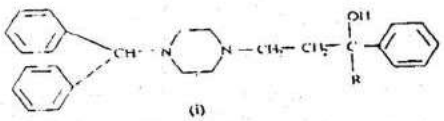
ABSTRACT

Four new derivatives of γ-(4-benzhydryl-1-piperaziny)-α -phenyl propanols were prepared using Grignard's reaction. They were isolated as solid bases and their structures elucidated using I.R. and ^{1} Hnmr spectroscopy. The compounds were screened for antispasmodic activity on guinea pig ileum, suing acetylcholine as the spasmodic agent. They all gave complete inhibition 80% maximal acetlcholine-induced contractions at microgram concentrations.

Keywords: *Benzhydrylpiperazine Propanols, Antipasmodic Activity, Grignard's Reaction, B-piperazinyl Keynotes.*

INTRODUCTION

Atropine is a tropic acid ester of tropine and is a known potent spasmolytic agent. However, the spasmolytic action of atropine cannot be made use of clinically because of the numerous other side effects of the drug on the nervous system. Realisation of this fact has led to a series of research works over the years for drugs, which spasmolytic properties predominate over the effect blood pressure and others. The earliest report in this direction was on certain substituted β-aminoalkylarylketones [1]. These were reported to possess antispasmodic action, but the quantitative pharmacological evaluation and the correlation of antispasmodic activity with the chemical structure were not given. In order to provide this. Denton [1] and co-workers, synthesized a series of substituted β-amino ketones after pharmacological evaluation, they found that six out of the thirty-seven substituted aminoketones studied equalled β-ethylaminoethyl diphenyl acetate dihydrochloride (trasentin) in antispasmodic ratings. Some of the transformations they made had effects on the antispasmodic action of the ketones. As a result, these authors in a late study [2] transformed the ketones to the alcohol and found that the addition of an alkyl Grignard reagent to β-(1-piperidyl)-propiophenones, having no a-substituents, yielded teritary alcohols which generally have greater spasmolytic activities than the corresponding propiohenones. To study the effect of the amino function. Denton [3] synthesised a group of amino alcohols in which the amino groups were dimethylamino, diethylamino, piperidyl, morpholinyl, tetraisoquinolyl and 4-methyl-1-piperazinyl) propanol was of piperazine series. Shortly after Katz *et al* [4] described two series of γ-amino alcohols. Cymmerman-Craig and Harrison [5] reported that some teritary alcohols containing piperazine heterocycle in their molecules showed spasmolytic activity. Zaug and co-workers [6] also prepared and evaluated a group of teritary carbinols, which were generally of β-piperazinyl series. With a view to study the effect of replacement of carbonyl group of 4-benzyl-1-{β-benzoylethyl}piperazin and 1.4-bis{benzoylethyl}piperazine with tertiary alcohol moiety, Natova and Zhelyazkov [7] synthesised a series of piperazine-containing gamma amino alcohols but there was no communication as regards the pharmacological evaluation of the compounds. In all the literature reviewed, an obvious absence of information on the gamma benzhydryl propanols [1] was observed. We therefore undertool to synthesise compounds on the type [1] where R=H, CH_3, C_6H_5 so as to study the quantitative effect of the benzhydryl group on the spasmolytic activity of gamme-amino propanols and the influence of the various R groups.



(i)

Pieces of information on the secondary piperazine propanol derivative (R = H) were readily obtained in literature [8.9.10] but these were mainly on the methods of synthesis and isolation.

EXPERIMENTAL

Material and methods

Melting points (MP) were determined with the Thiele's apparatus or the Gallenkamp melting point apparatus and are not corrected. Proton nuclear magnetic resonance (^{1}H NMR) spectra were recorded on YNM-C-100s (Joel-Tokyo) spectrophotometer, working at a frequency of 100 MHZ. Chemical shifts were reported on δ scale (in ppm) relative to TMS (used as internal standard). Deuterated Chloroform ($CDCl_3$) was

used as the solvent. The samples were dried at temperatures not more than 60°C. Elemental analyses were carried out at LEUVEN Linkage laboratory of the Department of Soil Science. University of Nigeria Nsukka.

Infrared spectra of the compounds were recorded as 100% thin film for the oily products) or as 3mg/300mg concentration of the substance in KBr (for the solids). The ultra-violet spectra were recorded on spectronic 1201(MILTON ROY)

(1) 4-Benzhydryl-1-benzoylethyl) piperazine dihydrochloride (Mannich product)

Benzhydryl piperazine (24.7g) dissolved in 80 ml of ethanol (90%), was introduced in a three-necked flask equipped with two dropping funnels and a reflux condenser. The solution was acidified to pH 1.5. This was heated while stirring till the ethanol boiled. Acetophene (17.6ml) and paraformaldehyde (6g) were added in portions for a period of about 30min., at the end of which the reaction mixture was boiled for additional 2 hours. This yielded 33g (88%) of the dihydrochloride salt, Mp =183°C (lit. 183-184°C) [1] Dissolution of this salt in hot ethanol and its decomposition in aqueous ammonia gave 100% yield of the base Mp=91-92°C.

(2) Preparation of γ-(1-benzhydrylpiperaziny-α-phenyl propanol

A 0.045 mole proportion (18.38) of the above Mannich base was dissolved in 80-100 ml of ethanol and made alkaline with 20-25 ml of 3M NaOH. The mixture was treated in portions (with stirring) with a solution of 0.12 mole proportion (4.6g) of $NaBH_4$ in 60-70 ml of water, which has been made alkaline to pH 12 with 5M NaOH and refluxed for 2 hours, The ethanol was distilled off, the residue diluted with 80-90ml water, extracted with chloroform and dried with anhydrous Na_2SO_4 for two days. After decanting and distilling the solvent the raw base of the piperazinyl alcohol was obtained (99% yield), MP = 151°C (from ethanol) lit. 148 - 150°Cl10}, ^1H NMR (δvalue in ppm.) $CDCl_3$ 7.28 (m, 15H,3H.3ph): 4.84(i.IH.CHO); 4.18 (S.IH.Ph_2CH); 2.50 (m.NCH_2 I.R. (cm^{-1}) 711,750 775 (C_6H_5), 3200 (OH) 1135 (C-OH. KBr film) 2760, 2810 (NCH_2) 1465, 1500, 1600, 2975, 3025, 3025 (Ar) λmax = 220 (in octanol) R^F value - 0.51 (Benzene/ethylacetate, 7:3).

(3) γ -(4-benzyhydryl-piperazinyl-a-phenyl-α-methyl propanol

A 4.4g (10.036 moles) sample of 4-benzhydryl-l- (Benzoylethyl) piperazine dihydrochloride) Mannich product) was added in portions to an already prepared and cooled methyl magnesium iodide (prepared from 2.10g (10.09 moles) magnesium and 12.8g (10.09 moles) methyl iodide. After the addition of the finely ground β-keto benzhydryl piperazine, the reaction mixture was boiled for an additional 2 hours and then cooled. Cooling was immediately followed by hydrolysis with saturated solution of ammonium chloride and ice blocks. The product was filtered, washed thoroughly with water and dried. Yield of the crude product was 14.55 (85%) M.P - 159 - 160°C (from ethanol) Anal. Calculated for $C_{27}H_{32}N_2O$ N, 7.00 C,81.00 H, .8.00 found N,.6.90. ^1H NMR: 7.30 (m. 15H $3C_6H_5$,,4.2 (S. IH Ph_2 CH_3) 2.33 (m. 12H $6CH_2$) 0.60 (s. 3H. CH_3) I.R. (cm^{-1}) 711. 750, 775 C_6H_5), 3200 (OH) 2760, 2810 (NCH_2), 1465 1500 1600, 2975, 3025, 3075 (Ar) λmax = 220 (in Octanol)

(4) γ -(4-benzhydryl-piperazinyl)-a ethyl)-propanol

A 13.9g. (0.035 moles) samples of 4-benzhydryl-I-benzoyl ethyl) piperazine dihydrochloride added in portions, in form of a fine powder, to an already prepared and cooled ethyl magnesium bromide (prepared from 2.1g of magnesium and 9.6g of ethyl bromide). The rest of the procedure was as described in experiment [3] above. In this preparation addition of ethyl bromide to magnesium and the subsequent Gringnard's reaction lasted for 4/½ hours. The raw product had a yellowish-brown appearance, which after hydrolysis gave a solid (15.15g. 80%) with melting point of 163.-165°C (from ethanol) λmax 212nm. Anal calculated for $C_{28}H_{34}N_2O$ C,18.16, H, . 8.12, .N. 6.76 found. N. 7.00. ^1H NMR (CDCl$_3$,. (δ value in ppm) 7.30 (m. 15H $3C_6H_5$) 4.10 (s. IH.Ph_2CH) 1.50 - 2.70 (m. 14H. $7CH_2$). 0.60 (l.$3H_2CH_3$). I.R (cm^{-1}). 711.750, 775, (C_6H_5) 3200 (OH), 2760, 2810 (NCH_2) 1465, 1500, 1600, 2975, 3025, 3075 (Ar.)

(5) γ -(4-benzhydryl-piperazinyl)-α ,α - diphenyl propanol

This was similarly prepared by the addition of 12.1g of the Mannich product in experiment [1] to phenyl magnesium bromide prepared from 12.56g. of bromobenzene and 1.92g of magnesium. The Mannich base was also in fine powdery form. The bath temperature was maintained at 60 - 70°C throughout the reaction. This was done to ensure moderate boiling of the either, since side products are produced when the boiling is vigorous. The hydrolysis of the adduct was similarly achieved as above. A solid base was obtained, which gave a negative result with the sodium nitroprusside test for CH_2CO group, an indication that the original ketone had been converted to alcohol. The product is insoluble in ether. Advantage was taken of this to removed the unreacted halide by washing with ether. M.P. - 165°C (from ethanol) ymax = 223nm (in Octanol). ^1H NMR ($CDC1_3$ δ value in ppm) 8.00 (s. 111 O11) (D_2O exchangeable): 7.30 (m. 20H, $4C_6H_5$): 4.20 (s. lH, Ph_2CH): 2.40 (s.12H. $6CH_3$). Anal Calculated for $C_{24}H_{34}N_{30}$ C.83.12. H. 7.36.N.6.06. Found N. 6.30. IR (cm^{-1}) 711.750 (C_6H_5) 3200 (OH) 1140 (C-OH. KBr film used). 2760 2760 2810 (NCH_2), 1465. 1600 3025 3075 (Ar).

(6) γ-benzhydryl-piperazinyl)-α-phenyl-α-benzyl propanol

This compound was similarly prepared by the addition of 12.1g of 4-benzhydryl-l-(β - benzoylethyl) piperazine dihydrochloride of the Mannich base to benzyl magnesium chloride (Prepared from 10.1 g. (0.08 moles) of magnesium). The rest of the procedure was as described in Experiment [2]. The reaction time was 6 hours. The yield of the piperazine propanol was 19.8g (88%) M.P = 175 - 176°C (from ethanol) λmax = 212nm Anal. Calculated for ($C_{33}H_{36}H_2O$ C. 83.19 H. 756 N. 5.88. Found N. 6.00. ^1H NMR ($CDCl_3$ δ value in ppm) 7.20 (m.20H 4Ph), 4.10 (s. IH. Ph_2CH) 2.90 (m.2H. $PhCH_2C$), 2.20 (m. 12H. $6CH_2$) I.R. (cm^{-1}). 711. 750. 775 (C_6H_5), 3200 (OH), 1140 (C-OH, KBr film used) 2760 2810 (NCH_2). 1465.1600, 3025, 3075 (Ar). Given in parentheses are the types of signal. No. of hydrogen involved and the group responsible for the signal s = singlet, d = doublet, m = multiplet, t = triplet, ph = phenyl.

Effect of the synthesized product on isolated Guinea pig ileum (Antispasmodic screening)

The guinea pigs were starved for 24 hours and killed after stunning. A segment (2 - 3cm) of the ileum was suspended in an organ bath (10ml) containing Tyrode solution at 32°C, aerated with air. The set-up was allowed 60 min. to equilibrate. The effect of increasing concentrations of the products (dissolved in 0. IN HCI) on contractions induced by acetylcholine were investigated and recorded on Ugo-Basil Universal oscillograph through an isotonic transducer.

RESULTS AND DISCUSSION

Four compounds of the benzhydryl piperazine propanol derivatives were prepared (gamma-(l-benzhydrylpoperaziny)-α-phenyl-propanol was prepared by reduction of 4-benzhydryl-l-(β-benzoylethyl) piperazine dihydrochloride with sodium borohydride ($NaBH_4$). The above mannich product was prepared from benzhydryl piperazine. Acetophenone and paraformaldehyde. ie. Reduction of the Mannich product using $NaBH_4$. was found more convenient, involving simply boiling in ethanol. Very good yield of the reduction product was obtained. An alternative approach would have been to use $LiAlH_4$ reduction but this requires very stringent reaction conditions and leads to comparatively lower yield of the secondary propanol.

The tertiary piperazinyl propanols were obtained in very good yields using Grignard's reaction. Purification was achieved through repeated recrystallisation. Using thin layer chromatography performed on Silica gel checked the purity.

In the I.R. spectra of the compounds described a conspicuous absence of absorption signal of the C=Ogroup (at 1720cm^{-1}) of the original β - keto piperazine was observed, while a broad band for OH group was observed around 3200cm^{-1} and another around 1150^{-1}) (KBr used) for the C-OH bond.

From the pharmacological evaluation, it was found that these compounds gave complete inhibition of 80% sub maximal contractions of acetylcholine at microgram concentrations. The inhibition was found to be the competitive type since maximum acetylcholine-induced contractions were normally recovered (after full inhibition) by used of higher doses of acetylcholine. It was found that substitution of benzyhydrl piperazine group (otherwise known as diphenylmethyl group) on the second nitrogen of the gamma-piperazinyl alcohol does not lead to loss of activity, in spite of the substituent groups introduced through the Grignard's reaction. The detailed quantitative antispasmodic evaluation of these compounds and the correlation of their structures with their biological activity will be published later.

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