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Synthesis of Some Unsymmetrical Ester Derivatives of γ-(4-Substituted piperazin-1-yl)-α-phenyl propanols with Antispasmodic Activity

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Abstract

Six new ester derivatives of γ-(4-substituted piperazinyl)-α-phenyl propanol were prepared by esterification of the γ-piperazinyl propanols.

The derivatives were methyl, ethyl, phenyl and benzyl esters, and they were obtained in good yields using a solid–liquid phase transfer catalysed esterification method. The nitrogen content of the new derivatives was also determined. Studies using isolated guinea-pig ileum showed that the derivatives possessed varying degrees of antispasmodic activity.

Of the compounds evaluated, the ethyl ester of γ-(4-benzyl piperazin-1-yl)-α-phenyl propanol showed the greatest antispasmodic activity.

It is known that very small changes in the structure of a given drug molecule can lead to radical changes in its elicited biological activity (Janssen & Jageneal 1957; Daniels & Jorgensen 1977). Several groups have reported that drugs containing the γ-amino alcohol moiety in their molecules usually possess antispasmodic effects (Denton et al 1949a, b; Katz et al 1954; Janssen & Jageneal 1957). Atropine, a tropic acid ester of tropine (γ-amino alcohol), represents a cyclic ester. Atropine possesses some antispasmodic properties, however its usefulness is limited because of the numerous other effects of the drug. As a result several open chain γ-amino alcohols have been synthesized (Katz et al 1954; Zaugg et al 1958; Natova & Zhelyazkov 1973). Attention has been directed towards the piperazine derivatives (i.e. where the amino group is a piperazine nucleus. It has been reported that γ-amino alcohols containing a piperazine nucleus as the amino portion retained antispasmodic properties (Cymmerman & Harrison 1956; Zaugg et al 1958; Natova & Zhelyazkov 1973; Osadebe 1992). We therefore proposed to synthesize a series of open chain γ-piperazinyl propanols esters in which the piperazine nucleus is substituted at N^4 with benzyl and benzhydryl groups (R_1), and R_2 represents methyl, ethyl, phenyl and benzyl groups (Figure 1). Six new ester derivatives of γ-piperazinyl propanol were prepared using standard esterification procedures (Szeja 1980) and also a phase-transfer catalysed esterification procedure (Dehmlow & Dehmlow, 1980; Osadebe 1993) (Figure 2). The antispasmodic activity of the series was evaluated using isolated guinea-pig ileum.

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Materials and Methods

Melting points were determined on a Thiele's apparatus or Gallenkamp melting point apparatus, and are uncorrected. ^{1}H NMR spectra were recorded on a Jeol YNM-C 100 spectrophotometer (100 MHz) using $CDCl_3$ as solvent. Chemical shifts (δ ppm) refer to tetramethylsilane which was used as an internal standard. The samples were dried at temperatures not greater than 60°C. Elemental analyses were carried out at the Leuven Linkage Laboratory of the Department of Soil Science, University of Nigeria. IR spectra were recorded as 100% thin films (for oily products) or as 3 mg/300 mg concentration of the substance in KBr (for solids). UV spectra were recorded on a Spectronic 1201 (Milton Roy).

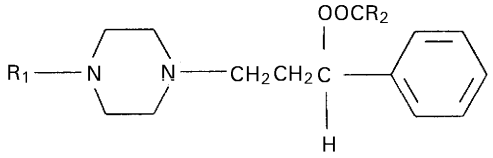
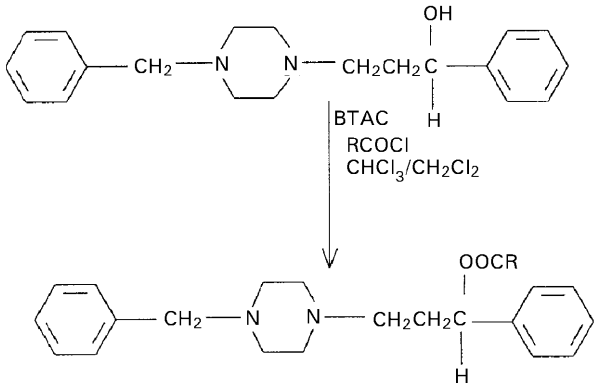


Figure 1. Structure of proposed open chain γ-piperazinyl propanols esters. The piperazine nucleus is substituted at N^4 with benzyl and benzhydryl groups (R_1), and R_2 represents methyl, ethyl, phenyl and benzyl groups.



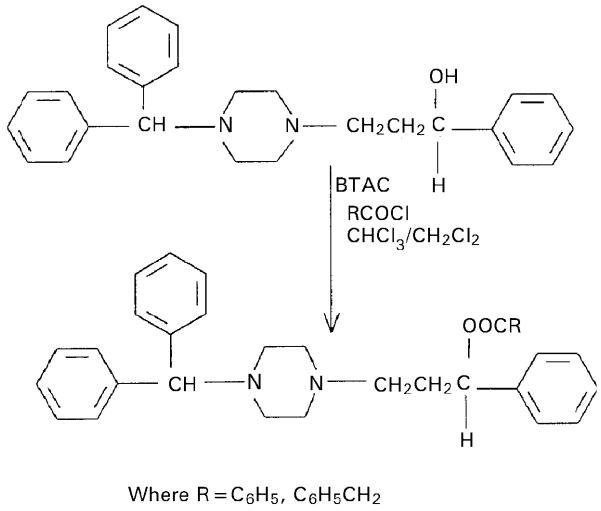


Figure 2. Schematic representation of the phase-transfer catalysed esterification procedure. BTAC, benzyltriethyl ammonium chloride; RCOCl, acyl chloride.

Synthesis

Preparation of γ-(4-benzyl piperazin-1-yl)-α-phenyl propanol. The dihydrochloride salt of 1-benzyl-4(β-benzoylethyl) piperazine (Natova & Zhelyakov 1973; Osadebe 1993; Valenta et al 1981) (13·9 g, 0·045 mol), was dissolved in ethanol and made alkaline with 20–25 mL 5 M NaOH. A solution of 0·12 mol $NaBH_4$ (4·5 g) in 60–70 mL water, which had been made alkaline (pH 10) with 5 M NaOH, was added in portions with stirring and the mixture was boiled for 2 h. The ethanol was distilled off, the residue diluted with 80–90 mL water, extracted with benzene or chloroform and dried with anhydrous Na_2SO_4 for 2 days. After distilling off the solvent, the crude base of the piperazinyl alcohol was obtained. Yield = 14·0 g (98·7%); mp of the base = 75°C (from petroleum ether); lit. mp = 65–75°C (Zikolova & Ninov 1972); mp of the oxalate salt = 225–226°C; R_f = 0·59 (butanol 100%).

Preparation of γ-(4-benzhydryl piperazin-1-yl)-α-phenyl propanol. The preparation of γ-(4-diphenylmethyl piperazinyl)α-phenyl propanol followed the same procedure as above. After decanting and distilling the solvent, the raw base of the piperazinyl alcohol was obtained. Yield = 13·8 g (99%); mp = 149–151°C (from ethanol); lit. mp = 148–150°C (Valenta et al 1981). ^{1}H NMR (δ ppm): 7·28(M, 15H, 3Ph); 4·84 (t, 1H, CHO); 4·18(s, 1H Ph_2CH); 2·50 (M, 10H, NCH_2). IR (cm^{-1}): 711, 750–775 (C_6H_5), 3200(OH) 1135 (C–OH, KBr film) 2760, 2810(NH_2) 1465, 1500, 1600, 2975, 3025, 3075 (Ar); λ_{max} = 220 (in octanol); R_f = 0·51 (benzene–ethylacetate, 7 : 3)

Preparation of γ-(4-benzyl piperazin-1-yl)-α-phenyl propanol acetate. A mixture of the alcohol (20 g, 0·047 mol), the phase-transfer catalyst, benzyltriethyl ammonium chloride (2·14 g, 0·01 mol), and anhydrous sodium carbonate (15 g) in 35–40 mL dichloromethane was treated with a solution of acetyl chloride (4·89 mL, 0·069 mol) in 5 mL of the same solvent for 15–20 min. The inorganic salts were then filtered off and the residue washed 3- or 4- times with 25 mL water, and dried over anhydrous sodium sulphate for 48 h. The solvent was then evaporated. The dry oily base of the ester was obtained (yield 91·5%). The dihydrochloride (SHCl) salt of the ester was obtained by redissolving the oily base in chloroform or ether and treating with excess of a saturated solution of dry hydrogen chloride gas in ether. The yield of the SHCl salt was 91%; mp = 206–207°C (dec) (from isopropanol); R_f = 0·31 (silica gel; benzene–ethylacetate, 7 : 3). Calculated for $C_{22}H_{30}H_2O_2Cl_2$: N, 6·59; found: N, 6·50. ^{1}H NMR (δ ppm): 7·30 (s, 10H, ph); 5·76 (t, 1H, HCO); 3·44 (s, 2H, $PhCH_2$) 1·90 (s, 3H, CH_3); 2·30 (M, 12H CH_2). IR (cm^{-1}): 711, 750, 775 (C_6H_5), 2760 2810, (NH_2) 1405, 1500, 2975, 3025 3078 (Ar) 1745 (CO, ester).

Preparation of γ-(4-benzyl piperazin-1-yl)-α-phenyl propanol propanoate. A mixture of γ-(4-

benzyl piperazin-1-yl)-α-phenyl propanol (20 g, 0·046 mol), benzyltriethyl ammonium chloride (2·14 g, 0·01 mol) and anhydrous sodium carbonate (15 g) in dichloromethane (35–40 mL) was treated with a solution of propanoyl chloride (6·82 mL, 0·078 mol) in 5 mL of the same solvent for 15–20 min. The mixture was boiled under reflux for 3·5 h and then cooled. The inorganic salts were then filtered off and the residue washed with the organic solvent. The organic layer was washed 3- or 4-times with 25 mL water in a separatory funnel and dried over anhydrous sodium sulphate for 48 h. The solvent was then evaporated in-vacuo. A dry oily base was obtained. It was redissolved in chloroform and treated with excess of a saturated solution of dry hydrogen chloride gas in ether to give the 2HCl salt (yield 20·8 g, 86%); mp = 228°C (dec) (from isopropanol); $R_f = 0{\cdot}45$ (silica gel; benzene–ethylacetate, 7 : 3). Calculated for $C_{23}H_{32}N_2Cl_2$: N, 6·38; found: N, 6·31. ^{1}H NMR (δ ppm): 7·28 (m, 10H, 2Ph); 5·78(t, 1H, CH-O): 3·40(s, 2H, $pHCH_2$) 2·12(m, 14H, CH_2); 1·00 (t, 3H, CH_3). IR (cm^{-1}): 711, 750, 775 (C H) 2760, 2810 (NH_2) 1465, 1500, 2975, 3025, 3075 (Ar), 1745 (Co, ester).

Preparation of γ-(4-benzyl piperazin-1-yl)-α-phenyl propanol benzoate. A mixture of γ-(4-benzyl piperazin-1-yl)-α-phenyl propanol (20 g, 0·046 mol), benzyltriethyl ammonium chloride (2·14 g, 0·01 mol) in chloroform was treated with a solution of benzoyl chloride (9·01 mL, 0·0669 mol) in 5 mL of the same solvent for 20 min. The mixture was boiled under reflux for 1·5 h and then cooled. After cooling, the inorganic salts were filtered off and the residue washed with the organic solvent. The organic layer was washed 3 times with 25 mL water in a separatory funnel and dried over anhydrous sodium sulphate for 48 h. After filtration, the solvent was evaporated in-vacuo. A dry oily base of the ester was obtained. The 2HCl salt was obtained by redissolving the oily base in ether and treating with excess of a saturated solution of dry hydrogen chloride in ether. Yield = 24·0 g (76·4%); mp = 218°C (dec) (recrystallized from ethanol); $R_f = 0{\cdot}72$ (benzene–ethylacetate, 7 : 3). Calculated for $C_{27}H_{32}N_2O_2Cl_2$: N, 5·75; found: N, 5·76. ^{1}H NMR (δ ppm) of the base: 8·00(d, 2H, OH of Ph) 7·24 (m, 13H, Ph); 2·10 (m, 12H, $5NCH_2 + C{=}CH_2{-}C$), 6·00(t, 1H, CH−O) 3·44(s, 2H, NCH_2Ph). IR (cm^{-1}): 711, 750, 775, (C_6H_5), 2760, 2810 (NH_2) 1465, 1500, 2975, 3025, 3075 (Ar), 1745 (CO, ester).

Preparation of γ-(4-benzyl piperazin-1-yl)-α-phenyl propanol phenylacetate. A mixture of γ-(4-benzyl piperazin-1-yl)-α-phenyl propanol (20 g, 0·046 mol), benzyltriethyl ammonium chloride (2·14 g, 0·01 mol) and anhydrous sodium carbonate (15 g) in chloroform (35–40 mL) was treated with phenylacetyl chloride (10·33 mL, 0·078 mol) in 5 mL of the same solvent for 15–20 min. The mixture was boiled under reflux for 1·5 h and then cooled. The inorganic salts were then filtered off and the residue washed with the organic solvent. The organic layer was washed 3 times with 25 mL water in a separatory funnel and then dried over anhydrous sodium sulphate for 48 h, after which the solvent was evaporated in-vacuo. A dry oily base of the ester was obtained which crystallized at room temperature. Yield = 25·8 g, (98·5%); mp = 79–80°C (recrystallized from ethanol); $R_f = 0{\cdot}49$ (chloroform, 100%). Calculated for $C_{34}H_{36}N_2O_2$: N, 5·50; found: N, 5·41. ^{1}H NMR (δ ppm) of the base: 7·20(m, 10H, Ph); 5·74(t, 1H, HC-O) 4·12(s, 1H, Ph_2CH) 3·45(s, 2H, CH_2CO). IR (cm^{-1}): 711, 750, 775 (C_6H_5), 2760, 2810 (NH_2), 1465, 1500 2975, 3025, 3075 (Ar), 1745 (CO, ester).

Preparation of γ-(4-benzhydryl piperazin-1-yl)-α-phenyl propanol benzoate. Anhydrous Na_2CO_3 (7 g) was suspended in dry chloroform (40 mL) and stirred well until a stable suspension formed. The solution of the alcohol (20 g, 0·046 mol) in chloroform (5–6 mL) was added to the reaction vessel and stirred for approximately 10 min, after which a solution of benzoyl chloride (13·4 mL, 0·12 mol) in chloroform (8 mL) was added in portions from a dropping funnel (fitted with $CaCl_2$ tube). The mixture was boiled under reflux for 3·5 h. After cooling, the inorganic salts were filtered off and the solid residue washed with chloroform. The organic layer was washed 3 times with 25 mL water and dried over anhydrous sodium sulphate. The sodium sulphate layer was decanted and, after washing with more of the dry solvent, the solvent was evaporated in-vacuo. An oily base of the ester was obtained which solidified at room temperature. Yield = 4·6 g (97%); mp = 151°C (recrystallized from acetone); $R_f = 0{\cdot}87$ (benzene/ethylacetate). Calculated for $C_{33}H_{34}N_2O_2$: N, 5·62; found: N, 5·50. ^{1}H NMR (δ ppm): 8·08 (d, 2H, Ortho H of Ph); 7·30(m, 18H, Ph); 2·10(m, 12H, $5NCH_2 + C{-}CH_2{-}C$); 6·10 (t, 1H, HC−O) 4·20 (s, 1H, Ph_2CHN). IR (cm^{-1}): 711, 750, 775 (C_6H_5) 270, 2810 (NH_2, 1465, 1500, 2975, 3025 (Ar), 1745, (CO, ester).

Preparation of γ-(4-benzhydryl piperazin-1-yl)-α-phenyl propanol phenylacetate. A mixture of γ-(4-benzhydryl piperazin-1-yl)-α-phenyl propanol (20 g, 0·046 mol), benzyltriethyl ammonium

chloride (2·14 g, 0·01 mol) and anhydrous sodium carbonate (15 g) in chloroform (40 mL) was treated with a solution of phenylacetyl chloride (12·8 g, 0·078 mol) in 5 mL of the same solvent for 15–20 min. The mixture was boiled under reflux for 2 h and then cooled. The inorganic salts were then filtered off and the residue washed with organic solvent. The organic layer was washed 3 times with 25 mL water in a separatory funnel and then dried over anhydrous sodium sulphate for 48 h. After filtering and washing with dry chloroform, the solvent was evaporated to dryness in-vacuo. A dry oily base was obtained which crystallized at room temperature. Yield = 25·8 g (98·5%); mp = 79–80°C (recrystallized from ethanol); $R_f = 0{\cdot}49$ (chloroform, 100%). Calculated for $C_{34}H_{36}N_2O_2$: N, 5·50; found: N, 5·41. ^{1}H NMR (δ ppm) of the base: 7·20(m, 10H, Ph); 5·74(t, 1H, HC−O) 4·12 (s, 1H, Ph_2CH) 3·45 (s, 2H, CH_2CO). IR (cm^{-1}): 711, 750, 775 (C_6H_5), 2760, 2810 (NH_2), 1465, 1500, 2975, 3025, 3075 (Ar), 1745 (CO, ester).

Antispasmodic activity

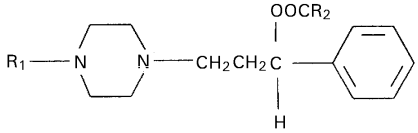
Mature guinea-pigs of either sex (350–400 g), were purchased locally. The guinea-pigs were fasted for 24 h before the experiment and then killed by stunning. A segment of the ileum (approx. 3 cm) was suspended in an organ bath containing Tyrode solution of the following composition (mM): 137 NaCl; 2·4 KCl; 1·8 $CaCl_2$; 1·0 $MgCl_2$; 0·2 $NaHPO_4$; 11·9 $NaHCO_3$ and 5·5 glucose. The solution was maintained at 32°C and aerated using an automatic electric aerator. After an equilibration period of approximately 60 min at a resting tension of 0·5 g, a full dose–response relationship was established for acetylcholine. The effects of increasing concentrations of each derivative on the contractions induced by a submaximal (80%) concentration of acetylcholine ($1{\cdot}35 \times 10^{-8}$ M) were investigated. The effects were recorded on an Ugo-Basile universal oscillograph through an isotonic transducer. The dose that produced 50% inhibition of acetylcholine-induced contraction (ID50) was estimated for each derivative (Van Rossum 1949).

Results and Discussion

The derivatives were obtained in good yields (92–99%) by reacting γ-(4-benzyl piperazin-l-yl)-α-phenyl propanol and γ-(4-benzhydryl piperazin-l-yl) propanol, respectively, with acyl chloride in the presence of benzyltriethyl ammonium chloride. Only γ-(4-benzhydryl piperazin-l-yl)-α-phenyl propanol benzoate was prepared using the standard esterification procedure (without the catalyst). The γ-(4-benzyl piperazin-l-yl)-α-phenyl propanol and γ-(4-benzhydryl piperazin-l-yl)-α-phenyl propanol used in the esterification were prepared by reduction of their corresponding β-ketopiperazines (Mannich bases) using an alcoholic solution of $NaBH_4$ at room temperature. The optimum duration of each experiment was determined by removing samples from the reaction vessel and subjecting them to routine thin-layer chromatography (Osadebe 1993). For the IR spectra of the esters, there was a disappearance of the OH absorption at 3200–3350 cm^{-1}, and the emergence of the strong carbonyl band of the esteric group at 1745 cm^{-1}.

The results of the antispasmodic evaluation of the esters, based on the inhibition of acetylcholine-induced contractions of guinea-pig ileum (ID50) are shown in Table 1. Compounds that were soluble in distilled water or 0·1 M HCl were tested quantitatively. Quantitative evaluation of the two benzhydryl propanol esters was hindered by their insolubility. All the esters showed an inhibitory effect against acetylcholine-induced contractions. Of the three esters evaluated, the most potent antispasmodic effect was exhibited by the γ-(4-benzyl piperazin-l-yl)-α-phenyl propanol propanoate (ID50 = 149·42 ng). When R_1 was changed from an ethyl group to a phenyl group, there was a sharp reduction in potency from 149·42 to 1949·84 ng. Replacement of the phenyl group by a benzyl group increased antispasmodic activity (ID50 646·51 ng). The antispasmodic activity of the esters may therefore be related to their polarity or aqueous solubility since the order of polarity for the R_2 substitutent is C_2H_5, $C_6H_5CH_2$, C_6H_5. These

Table 1. Inhibitory effect of some γ-piperazinyl esters against acetylcholine-induced contractions of isolated guinea-pig ileum.



Compound	Product	R_1	R_2	ID50 (ng)
1	E98 : 2HCl	$C_6H_5CH_2$	C_2H_5	149·42
2	E99 : 2HCl	$C_6H_5CH_2$	C_2H_5	1947·84
3	E96 : 2HCl	$C_6H_5CH_2$	$C_2H_5CH_2$	646·51
4	E102 : base	$(C_6H_5)_2$ CH	C_2H_5	–
5	E95 : base	$(C_6H_5)_2$ CH	$C_2H_5CH_2$	–

ID50 is the dose that produced 50% inhibition of acetylcholine-induced contractions.

esters showed good antispasmodic activity causing complete inhibition at microgram concentrations.

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