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Synthesis and pharmacological action of some *N*-alkyl morpholines and their salts

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The preparation is described of some 2-hydroxy-2- and 4-alkylmorpholines by ring closure of the corresponding phenacyl hydroxyalkylamines. The influence of structure upon the ring closure reaction is examined and the weak pharmacological action of the title compounds on leptazol convulsions, the autonomic nervous system and in the mouse hot-plate test is discussed in relation to the reversed esters of pethidine.

INTRODUCTION of an oxygen atom into the heterocyclic ring structure of the reversed esters of pethidine (I) has been investigated by Lutz & Jordan (1949) and the effect of this change upon the differences in pK_a between piperidines and morpholines has been discussed (Beckett, 1956). The reduction in pK_a is about 2·6 and should result in a much greater proportion of compound in the unionized form at physiological pH values.

The 2,2-substituted morpholines do not have the same relation between the phenyl group and the nitrogen atom as do the reversed esters of pethidine but they are analogues of the 3,3-substituted piperidine compounds (II) whose analgesic action has been reported (McDonald, Woolfe & others, 1946; Bergel, Hindley & others, 1944). We therefore investigated the synthesis of morpholines of structure (III, R^1 R^2 R^3 = H, alkyl, aryl, aralkyl) and of their salts. The general method used for the synthesis was the reaction of a phenacyl bromide with the appropriately substituted amino-alcohol (Lutz & Jordan, 1949; Cromwell & Tsou, 1949): the phenacylamino-alcohols (IV) formed initially, cyclized spontaneously to the hemi-ketal structures (III). Compounds prepared by this method are shown in Table 1. Structures III and IV are isomeric and the allocation of structure to the products was made by examination of the infrared spectra in the solid state (Nujol mull). Structures such as III, showed sharp bands around 3350–3400 cm^{-1} arising from the tertiary hydroxyl group and did not show any characteristic carbonyl absorption band. In one case (IV, R^1=Ph, R^2=R^3=H) the open-chain compound only was isolated.

The structures proposed for the compounds were supported also by their ultraviolet absorption spectra (Fig. 1). Ring closure of the phenacyl amines, to morpholines, was accompanied by a large reduction of ϵ_{max} due to the loss of the carbonyl chromophore. Values of ϵ_{max} in ethanol are recorded for salts of the ring-closed compounds in Table 2. The cyclic morpholine structures proposed for the compounds in the solid state are therefore retained in alcoholic solutions of the bases and their salts.

2-Hydroxymorpholine compounds were formed from the phenacylamines irrespective of the nature of the group R^1 in (IV): the electronic effect of R^1 had therefore little influence on the ring closure reaction. The influence of the nitrogen substituent was more important since it was

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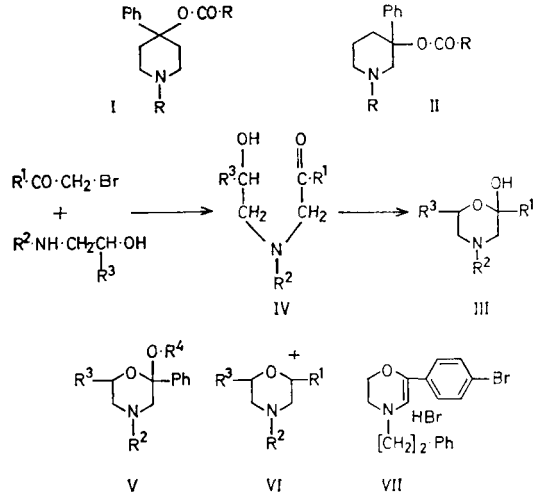


not possible to effect ring closure of the secondary amine (IV, R^1=Ph, R^2=R^3=H) and only the open-chain compound could be isolated. This hydroxyketone could not be converted to a morpholine compound by treatment with acid in anhydrous media, conditions normally used for the formation of ketals. We suggest that the ring closure reaction depends upon the adoption of a favourable conformation by the hydroxyalkyl side-chain. This conformation could be assisted by the steric effect of an additional substituent on the nitrogen atom. This hypothesis is supported by the ready ring closure of quaternary salts of bases such as

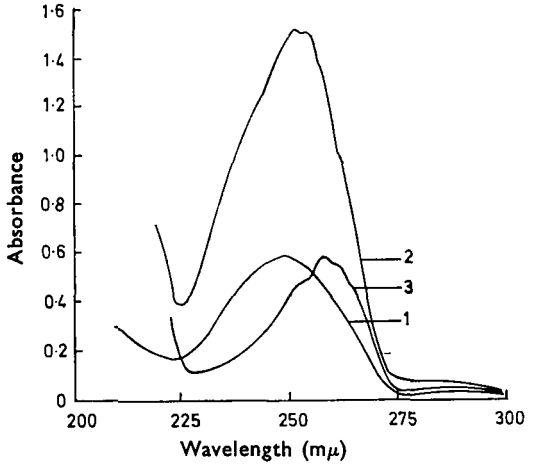
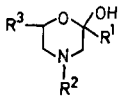


FIG. 1. Ultraviolet spectra of 1. Phenacyl bromide (9 mg/litre). 2. 2-Hydroxy-2-phenyl-4-phenylethylmorpholine hydrochloride (575 mg/litre). 3. 2-Ethoxy-2 phenyl-4-phenylethylmorpholine hydrochloride (555 mg/litre).

TABLE 1. PREPARATION AND PROPERTIES OF 2-HYDROXY-2,4,6-SUBSTITUTED MORPHOLINES

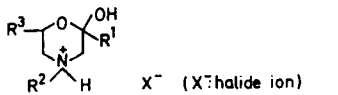


R¹	R²	R³	Starting material		Yield %	M.p.	Empirical formula	Found				Required			
			Amino-alcohol	α-Halo ketone				C	H	Br	N	C	H	Br	N
-Ph	-[CH_2]$_2$·Ph	H	2-phenylethyl-aminoethanol	Phenacyl bromide	69	90°	$C_{16}H_{21}NO_2$	76·6	7·7		5·2	76·3	7·5		4·9
-*p*-C_6H_4Br ..	-[CH_2]$_2$·Ph	H	2-phenylethyl-aminoethanol	*p*-Bromo-Phenacyl bromide	66	61°	$C_{16}H_{20}BrNO_2$	59·3	5·7	21·8	4·0	59·6	5·6	22·1	3·9
-Ph	-[CH_2]$_2$·Ph	-Me	1-(2-phenylethyl-amino)-2-propanol	Phenacyl bromide	71	75°	$C_{18}H_{23}NO_2$	77·0	7·9	Equiv. wt 296·3		76·8	7·8	Equiv. wt 297·4	
-Ph	-C_6H_{11} (cyclohexyl)	H	2-cyclohexyl-aminoethanol	Phenacyl bromide	77	86°	$C_{16}H_{23}NO_2$	73·5	8·7		5·5	73·8	8·5		5·4
-Ph	-Me	H	2-methyl-aminoethanol	Phenacyl bromide	66	52–53°*	$C_{11}H_{15}NO_2$			Equiv. wt 192·7				Equiv. wt 193·3	
-Ph	-Et	H	2-ethylamino-ethanol	Phenacyl bromide	77	54°*	$C_{12}H_{17}NO_2$			Equiv. wt 206·8				Equiv. wt 207·4	
-Ph	-CH_2·Ph	H	2-benzylamino-ethanol	Phenacyl bromide	66	61·5°*	$C_{17}H_{19}NO_2$			Equiv. wt 268·9				Equiv. wt 269·4	
-Me	-[CH_2]$_2$·Ph	H	2-phenylethyl-aminoethanol	Chloro-acetone	46	liquid n_D^{23} 1·5178	$C_{13}H_{19}NO_2$			Equiv. wt 220·4				Equiv. wt 221·3	

Infrared spectra (Nujol mull) of all compounds showed bands at 3200–3400 cm^{-1} (ν OH), 1030–1140 cm^{-1} ν C–O. Bands at 1620–1720 cm^{-1}, characteristic of ν C=O were not observed.

* Cromwell & Tsou (1949).

TABLE 2. PROPERTIES OF 2-HYDROXY-2,4,6-SUBSTITUTED MORPHOLINES HYDROHALIDES



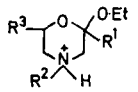
Salt	R¹	R²	R³	M.p.	Empirical formula	Found C	Found H	Found Br	Found Cl	Found N	Required C	Required H	Required Br	Required Cl	Required N
Hydrochloride* ..	Ph	-[CH₂]₂·Ph	H	150°	$C_{18}H_{22}ClNO_2$	67·4	6·9		11·0	4·3	67·6	6·9		11·1	4·4
Hydrochloride** ..	*p*-C_6H_4Br	-[CH₂]₂·Ph	H	149–150°	$C_{18}H_{21}BrClNO_2$	54·2	5·5	20·0	9·2	3·5	54·2	5·3	20·0	8·9	3·5
Hydrobromide	Ph	-[CH₂]₂·Ph	-CH_2	178°	$C_{19}H_{24}BrNO_2$	58·8	6·7	22·0		4·2	60·3	6·4	21·1		3·7
Hydrobromide† ..	Ph	C_6H_{11} (cyclohexyl)	H	194°	$C_{18}H_{24}BrNO_2$	56·3	6·9	23·2		4·1	56·1	7·1	23·3		4·1
Hydrobromide	Ph	Me	H	139°§	$C_{11}H_{16}BrNO_2$	Equiv. wt 273·0					Equiv. wt 274·2				
Hydrobromide	Ph	-CH_2·Ph	H	152°	$C_{17}H_{20}BrNO_2$	Equiv. wt 348·0					Equiv. wt 350·3				
Hydrochloride	Me	-[CH₂]₂·Ph	H	159°	$C_{18}H_{20}ClNO_2$	62·5	8·2		13·9	4·7	60·6	7·8		13·8	5·4

* λ_{max} 251 mμ, ε_{max} = 900 (methanol)
** λ_{max} 260 mμ, ε_{max} = 950 (methanol)
† λ_{max} 250 mμ, ε_{max} = 700 (methanol)

Infrared spectra (Nujol mull) of all compounds showed bands at 3200–3400 cm^{-1} (ν OH), 1040–1140 cm^{-1} (ν C–O) and 2500–2700 cm^{-1} (ν NH, protonated tertiary amino group).

§ Cromwell & Tsou (1949).

TABLE 3. PROPERTIES OF 2-ETHOXY-2,4,6-SUBSTITUTED MORPHOLINES HYDROHALIDES



X^- (X^- halide ion)

Salts	R^1	R^2	R^3	M.p.	Empirical formula	Found C	Found H	Found Br	Found Cl	Found N	Required C	Required H	Required Br	Required Cl	Required N
Hydrochloride* ..	Ph	-$[CH_2]_2$·Ph	H	157–158°	$C_{20}H_{24}ClNO_2$	69·1	7·5		10·3	4·1	69·0	7·5		10·2	4·0
Hydrochloride	*p*-C_6H_4Br	-$[CH_2]_2$·Ph	H	184°	$C_{20}H_{25}BrClNO_2$	56·1	5·9	Total halogen as Cl 16·4		3·4	56·3	5·9	Total halogen as Cl 16·6		3·3
Hydrobromide	Ph	-$[CH_2]_2$·Ph	Me	175–176·5°	$C_{21}H_{26}BrNO_2$	62·4	7·0	20·0		3·6	64·6	7·2	20·4		3·6
Hydrobromide	Ph	C_6H_{11} (cyclohexyl)	H	198–199°	$C_{18}H_{26}BrNO_2$	58·7	7·6	21·9		3·9	58·5	7·4	21·6		3·8
Hydrobromide	Ph	Me	H	151°	$C_{13}H_{20}BrNO_2$	51·7	6·8	26·2		4·8	51·7	6·7	26·4		4·6
Hydrobromide	Ph	-CH_2·Ph	H	165°†	$C_{19}H_{24}BrNO_2$	Equiv. wt 377·5					Equiv. wt 378·4				
Hydrobromide	Me	-$[CH_2]_2$·Ph	H	158°	$C_{15}H_{24}BrNO_2$	54·5	7·3	24·3		4·2	54·6	7·3	24·0		4·4
Hydrobromide** ..	Ph	C_6H_{11} (cyclohexyl)	H	197°	$C_{19}H_{30}BrNO_2$	59·2	7·6	21·0		3·7	59·4	7·8	20·8		3·6
Hydrobromide** ..	Me	$[CH_2]_3$·Ph	H	149°	$C_{16}H_{26}BrNO_2$	55·2	7·7			4·2	55·8	7·6			4·0

* λ_{max} 257 mμ ε_{max} = 400 (in ethanol)
** 2-isopropoxy compounds

Infrared spectra (Nujol mull) of all compounds showed bands at 2500–2800 cm^{-1} (ν N–H, protonated tertiary amino-group) and 1020–1150 cm^{-1} (ν C–O). Bands at 3200–3500 cm^{-1} characteristic of ν O–H were not observed.

† Cromwell & Tsou (1949).

(IV) (Long & Schueler, 1954). The failure of secondary amines to ring close even in strongly acidic media indicates also that the —I effect of the protonated amino-group or of the quaternary group is relatively unimportant when compared with the steric effect of the extra substitution on the nitrogen atom.

The expected morpholine compound from *N*-phenacylaminoethanol (IV, R^1=Ph, R^2=R^3=H) was prepared as its ethyl ketal (V, R^2=R^3=H, R^4=Et) by hydrogenolysis of the corresponding benzyl compound (V, R^2=$-CH_2Ph$, R^3=H, R^4=Et) which was easily formed by ring closure of the open chain compound (IV, R^1=Ph, R^2=$-CH_2{\cdot}Ph$, R^3=H) followed by treatment with acidified ethanol. The ethyl ketal (V, R^2=R^3=H, R^4=Et) was stable as the hydrobromide, but hydrolysis with dilute acid removed the ethyl group to give the open-chain compound (IV, R^1=Ph, R^2=R^3=H). This reversion to the open-chain form agrees with the results of attempts to synthesize this compound from the secondary amine. Hydrolysis of this ketal was surprisingly slow and the final value of ϵ_{248} = 12,700 for the product was reached only after 16 hr. 2-Hydroxy-2-phenyl morpholine is therefore fairly stable, though it could not be made directly.

The 2-hydroxymorpholine compounds that were prepared reacted readily with alcohols in presence of traces of acid to form the alkyl ketals (Table 3). Ketal formation occurred quite readily when the bulky isopropyl group was being introduced and when the other 2-substituent was methyl, as in (III, R^1=Me, R^2=$CH_2{\cdot}CH_2{\cdot}Ph$, R^3=H) or phenyl, as in (III, R^1=Ph, R^2=cyclohexyl, R^3=H) but none of the other hydroxymorpholines of Table 2 formed an isopropyl ketal. The formation of ketals was shown by the disappearance of the tertiary hydroxyl adsorption band at around 3400 cm^{-1} in the infrared spectra. Since formation of acetals and ketals is acid-catalysed (Bell & Norris, 1941) and probably proceeds through carbonium ions, the hemiketals under discussion must readily form carbonium ions (VI) even when R^1 is methyl. The dehydration of hemi ketals such as (III, R^1=*p*Br.C_6H_4, R^2=$[CH_2]_2{\cdot}Ph$, R^3=H) to give the 2,3-dehydromorpholine derivative (VII), could also be interpreted in this way.

The possibility of diastereoisomer formation during the ring closure reaction was investigated by the preparation of (III, R^1=Ph, R^2=$[CH_2]_2{\cdot}Ph$, R^3=Me) but chromatography in a variety of systems using silica-gel or alumina plates gave only a single spot and no separation into diastereoisomeric pairs could be demonstrated. We suggest that either the ring closure reaction occurs by attack of the hydroxyl group on the carbonyl group in (IV) from one direction only, or, more probably, the ring-closed structure (III) is in equilibrium, in solution, with a small proportion of the open chain form (IV).

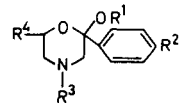
In the case of the homologous seven membered ring compound only the open-chain form could be isolated. Similarly, we could not prepare a five-membered ring compound by cyclization of *N*-2-hydroxyethyl-*N*-phenylethyl-*p*-nitro-benzamide. The presence of the *p*-nitro-group might be expected to increase the electrophilic character of the amide carbonyl

group but the product existed entirely in the open-chain form. Amide carbonyl groups are not usually susceptible to nucleophilic attack (in this case by –OH) and the failure of this ring closure is probably due to electronic effects rather than steric factors.

PHARMACOLOGICAL RESULTS

The compounds screened are shown in Table 4 and were administered as single doses of 100 mg/kg, orally to female mice. Administration of compounds 6, 7 and 8 produced convulsions at the dose levels used but compounds 1 and 2 had slight anti-convulsant action against leptazol. Compounds 3, 4 and 5 had no apparent effect at this dose level. The remaining compounds, 6, 7 and 8, showed some feeble action on the autonomic nervous system by producing blockade at ganglia and at post-ganglionic sites as shown by the inhibition of the responses to nicotine and to acetylcholine.

TABLE 4. MORPHOLINE DERIVATIVES TESTED PHARMACOLOGICALLY



Compound	R^1	R^2	R^3	R^4
1	H	H	$[CH_2]_2$·Ph	H
2	Et	H	$[CH_2]_2$·Ph	H
3	H	Br	$[CH_2]_2$·Ph	H
4	Et	Br	$[CH_2]_2$·Ph	H
5	H	H	$[CH_2]_2$·Ph	Me
6	Et	H	C_6H_{11}*	H
7	$CHMe_2$	H	C_6H_{11}*	H
8	Et	H	H	H

* Cyclohexyl

None of the compounds showed any analgesic activity in mice at this dose level when examined by the hot-plate method. The analogy between the 2,2-substituted morpholines and the 3,3-substituted piperidines is therefore not valid, nor does the analgesic activity of compounds of this type depend solely upon the relative pK_a values of the corresponding piperidines and morpholines (Hunter & Kourounakis, unpublished observations).

Experimental

Melting points were recorded on an Electrothermal capillary melting point apparatus and are uncorrected. Ultraviolet spectra were recorded using a Beckmann DK2 spectrophotometer, infrared spectra on a Unicam SP200 instrument and nuclear magnetic resonance spectra on a Perkin-Elmer R-10, 60 megacycle instrument with tetramethylsilane as internal reference in deuterated dimethylsulphoxide as solvent.

The amino-alcohols used as starting materials were prepared by published methods as follows, 2-phenylethylaminoethanol (Barbiere, 1940),

2-(1-phenyl-2-propylamino)ethanol (Rapp & Karnov, 1958), 1-(1-phenyl-2-propylamino)-2-propanol (Kiprianov & Khrapal, 1950), 2-benzylaminoethanol and 2-cyclohexylaminoethanol (Cope & Hancock, 1942), 3-(2-phenylethylamino)propanol (Hromatika, 1942) and *N*-phenacylethanolamine (IV, R^1=Ph, R^2=R^3=H) (Brighton & Reid, 1945).

1-(2-*Phenylethylamino*)-2-*propanol* was prepared by heating (1·5 hr at 100°) phenylethylamine (41·7 g), 1,2-epoxypropane (15 g) in water (5 ml). The product (26 g), a colourless liquid, had b.p. 96°–100°/0·2 mm η_D^{23} 1·5223. Equiv. wt: found 182, $C_{11}H_{17}NO$ requires 179.

The *hydrobromide*, crystallized in colourless needles from alcohol-ether, m.p. 88°. Found: C, 50·7; H 6·8; Br, 30·5; N, 5·2. $C_{11}H_{18}BrNO$ requires C, 50·7; H, 7·0; Br, 30·7; N, 5·4.

GENERAL METHOD FOR PREPARATION OF 2-HYDROXY-2,4-DISUBSTITUTED MORPHOLINES

Method I. A dry ethereal solution of the appropriate α-haloketone (1 mole in 200 ml) was added slowly to a similar solution of the amino-alcohol (2·2 mole in 500 ml) and the mixture kept 16 hr at 20°. The ether layer decanted from the precipitated salt was washed twice with saturated sodium chloride solution, dried and evaporated. The semi-solid residue was crystallized from ether–light petroleum (b.p. 40°–60°). The yields obtained and physical properties of the compounds prepared are shown in Table 1.

Method II. A 20% w/v solution of the haloketone (1 mole) in dimethylsulphoxide was added to a solution of the amino-alcohol (1·1 mole) in the same solvent (700 ml) at 45–50°. After 0·5 hr, triethylamine (1·0 mole) was added and stirring continued for 1 hr. The solution was poured into water and the product isolated by ether extraction as before.

Salts of the substituted morpholines (Table 2) were prepared by adding the calculated amounts of hydrogen bromide in isopropanol or hydrogen chloride in ethanol to a solution of the base in isopropanol. Crystallization was induced by the addition of ether and the salts were recrystallized from ethyl acetate-ethanol.

GENERAL METHOD FOR PREPARATION OF THE 2-ALKOXY 2,4-SUBSTITUTED MORPHOLINES

A salt of the appropriate 2-hydroxy-2,4-substituted morpholine was refluxed (4 hr) in absolute ethanol or isopropanol containing a few drops of a solution of hydrogen bromide or hydrogen chloride in the same alcohol. The solvent was evaporated to one-third volume and dry ether added to precipitate the salt of the ethoxy or isopropoxy ketal in quantitative yield. Ketals thus prepared are shown in Table 3.

The alkoxy group could be exchanged in (V, R^2=$-CH_2{\cdot}CH_2{\cdot}$Ph, R^3=H, R^4=$-CHMe_2$) and (V, R^2=$-C_6H_{11}$, R^3=H, R^4=$-CHMe_2$). The isopropoxy ketal hydrobromides were refluxed (6 hr) in ethanol containing a few drops of ethanolic hydrogen bromide solution. The salts of the ethoxy ketals were precipitated with ether as described above and recrystallized from ethanol-ethyl acetate in about 80% yield.

2-Ethoxy-2-phenyl-4-methyl morpholine. The free base was liberated from the ketal hydrobromide (V, R^2=Me, R^3=H, R^4=Et, hydrobromide) by treating it with saturated potassium carbonate solution followed by extraction with ether. Evaporation of the ether gave the product m.p. 57–58° (from ether–light petroleum, 40–60°). (Found, C, 70·7; H, 8·8. $C_{13}H_{19}NO_2$ requires C, 70·5; H, 8·7. Equiv. wt; found 220·7, required 221·3).

2-p-Bromophenyl-4-phenylethyl-2,3-dehydromorpholine hydrobromide (VII). 2-Hydroxy-2-*p*-bromophenyl-4-phenylethylmorpholine (III, R^1=*p*-Br·C_6H_4, R^2=$[CH_2]_2$·Ph, R^3=H) as the hydrobromide (1 g) was added to a mixture of isopropanol and ethyl acetate (5 ml, 1 : 1), a few drops of a 10% solution of hydrogen bromide in isopropanol added and the solution refluxed for 6 hr. Ether (20 ml) was added to the cooled solution and the precipitated salt filtered off and crystallized from isopropanol-ethyl acetate to give (VII) (0·4 g), m.p. 190°, ν_{max} (Nujol mull) 1650 cm^{-1} (C=C); τ 3·80 (D_6-DMSO) (olefinic proton); λ_{max} (ethanol) 320 mμ (ϵ_{max} 14,000). (Found, C, 51·0; H, 4·6; Br, 34·7; N, 3·4. $C_{18}H_{19}Br_2NO$ requires C, 50·8; H, 4·5; Br, 35·2; N, 3·3).

2-Ethoxy-2-phenylmorpholine hydrobromide (V, R^2=R^3=H, R^4=Et). 2-Ethoxy-2-phenyl-4-benzylmorpholine hydrobromide (V, R^1=CH_2·Ph, R^3=H, R^4=Et) (2·7 g) in absolute ethanol (150 ml) was shaken with hydrogen in presence of palladium-charcoal (0·2 g; 10%) at room temperature and pressure. When the calculated amount of hydrogen had been taken up the mixture was filtered and the solution concentrated to 20 ml. Addition of ether-ethyl acetate (20 ml, 1 :1) gave the product (1·9 g), m.p. 127·5°. Found: C, 50·1; H, 6·1; Br, 29·9; N, 5·1; $C_{12}H_{18}BrNO_2$ requires C, 50·0; H, 6·3; Br, 27·7; N, 4·9.

Phenacyl-(1-phenyl-2-propyl)ammonium nitrate. Phenacyl bromide (2 g), (±)-amphetamine (2·8 g) in ether (20 ml) were allowed to stand 24 hr, when a semi-solid precipitate formed. The ether was decanted and the residue well washed with further quantities of ether. From the combined ether extracts an oily layer separated and was removed. The residual ether solution was washed with water (2 × 15 ml), dilute acetic acid (2 × 15 ml of 2·5%) and finally with water (2 × 10 ml). Dilute nitric acid (60 ml, 0·25N) was added and the viscous phenacyl-(1-phenyl-2-propyl)ammonium nitrate layer separated from the resulting three-phase mixture. Trituration of the viscous oil with ethyl acetate–acetone (2 : 1) produced the pure *nitrate* (0·36 g) as colourless crystals, m.p. 126°. Found: C, 64·0; H, 6·1; N, 8·0; $C_{17}H_{20}N_2O_4$ requires C, 64·5; H, 6·4; N, 8·8. λ_{max} 248 mμ, ϵ_{max} = 13,000 (in ethanol).

N-2-Hydroxyethyl-N-phenylethyl p-nitrobenzamide. *p*-Nitrobenzoyl chloride (0·9 g) in dry tetrahydrofuran (10 ml) was added slowly to a solution of 2-phenylethylaminoethanol (2·7 g) in dry tetrahydrofuran (10 ml) and shaken occasionally over 2 hr at room temperature. The solvent was removed and the resulting oil treated with a mixture of ice and dilute hydrochloric acid (1 : 1). The solid mass obtained was well washed with saturated sodium bicarbonate solution and finally with water.

Crystallization from aqueous ethanol gave N-2-*hydroxyethyl*-N-*phenylethyl* p-*nitrobenzamide* (1·1g), m.p. 70°. Found: C, 64·7; H, 6·0; N, 8·9. $C_{17}H_{18}N_2O_4$ requires C, 64·9; H, 5·8; N, 8·9.

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