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Synthesis and resolution of the novel appetite suppressant 2-benzylmorpholine, a nonstimulant isomer of phenmetrazine

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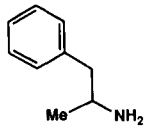
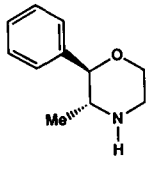
Abstract—The synthesis of 2-benzylmorpholine from allylbenzene together with its resolution into its (+)- and (−)-enantiomers is reported. Oral dosing of the racemate to dogs caused appetite suppression with an ED50 of 3 and 5·5 mg kg^{-1} at 1 and 2 h, respectively, after access to a meat meal. No stimulant activity was observed in dogs given oral doses of 200 mg kg^{-1} but the appetite suppressant effect in dogs declined during 20 days of chronic oral dosing at 10 mg kg^{-1}. Appetite suppression activity was shown to reside in the (+)-enantiomer.

Appetite suppressant drugs are used to assist patient compliance with calorie controlled diets (Reynolds 1989) and many, for example amphetamine (**1**) and phenmetrazine (**2**), show undesirable side effects (James 1987).

2-Benzylmorpholine (**3**) is a structural isomer of phenmetrazine and would be expected to show similar physical properties such as lipophilic character and basicity. It may thereby act at receptor sites such as the hypothalamus which control feeding behaviour (Bray 1979) and thus possess appetite suppressant properties. In addition unwanted side effects may be eliminated because of structural differences from **2**. We now report the synthesis, resolution into enantiomers and the appetite suppressant effects in dogs of 2-benzylmorpholine (**3**).



Structure 1



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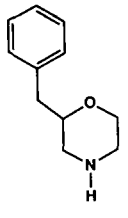

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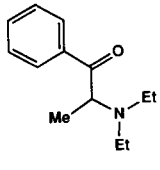

Structure 11

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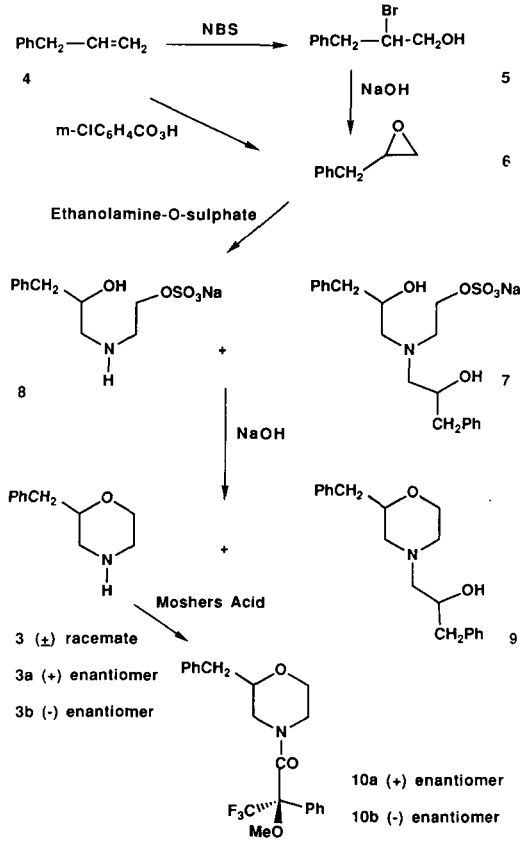

Scheme 1

Synthesis

Allylbenzene (**4**) (Scheme 1) was allowed to react with *m*-chloroperbenzoic acid to give the oxirane (**6**) in an unoptimized yield of 18%. An improved overall yield of 67% oxirane (**6**) was obtained when *N*-bromosuccinimide was used to give the intermediate bromohydrin (**5**), followed by ring closure with sodium hydroxide. Reaction of the oxirane (**6**) with ethanolamine-*O*-sulphate afforded a mixture of the tertiary base (**7**) and the desired ethanolamine (**8**). With sodium hydroxide 2-benzylmorpholine (**3**) and the *N*-substituted morpholine (**9**) resulted. 2-Benzylmorpholine was resolved with (−)- and (+)-dibenzoyltartaric acids separately, to give the enantiomers **3a** and **3b** which showed equal and opposite optical rotations in plane polarized light. The dibenzoyltartaric acid salts had identical melting points and the optical purity of enantiomers **3a** and **3b** was shown to be greater than 98% by HPLC examination of derivatives **10a** and **10b** made from the chiral reagent *R*-α-methoxy-α-(trifluoromethyl) phenylacetyl chloride (Dale 1969).

Preparative work. Melting points are uncorrected. ^{1}H NMR spectra were recorded on a Varian EM 390 (90 mHz) and mass spectra on an MS 902 Kratos (AEI) spectrometer. Optical

rotations were measured on an NDL 243 automatic polarimeter in a 2 mL cell. Assigned structures were supported by microanalyses and the characteristic NMR data quoted.

2-Benzyloxirane (**6**). (a) *m*-Chloroperbenzoic acid (170·8 g) was added during 3 h to a stirred mixture of sodium hydrogen carbonate (90·8 g), allylbenzene (94·4 g) in water (1000 mL) and dichloromethane (1300 mL) and stirring continued for 18 h. The dichloromethane phase was washed with saturated sodium hydrogen carbonate solution, sodium sulphite solution and brine. The dichloromethane was dried ($MgSO_4$) and evaporated to an oil which distilled to give 2-benzyloxirane (**6**) (19·3 g, 18%) b.p. 96–99 °C at 12 mm (compared with 88° at 9 mm, Castro & Noller 1946).

(b) *N*-Bromosuccinimide (100 g) was added to a stirred mixture of allylbenzene (66·3 g) in water (450 mL). After 48 h at room temperature (20 °C) the mixture was extracted with diethyl ether and the ether extract washed with brine, dried ($MgSO_4$) and evaporated to an oil (**5**). The oil was suspended in water (170 mL) and sodium hydroxide pellets (33·7 g) added. The mixture was heated at 65 °C (45 min), cooled to room temperature and diluted with water (500 mL). Extraction with diethyl ether and subsequent distillation gave (**6**) (49·5 g, 67%) b.p. 96–99 °C at 12 mm.

(±)-*2-Benzylmorpholine* (**3**). Ethanolamine-*O*-sulphate (58·8 g) was added to a mixture of 2-benzyloxirane (**6**) (13·4 g), 16 M sodium hydroxide solution (32 g) and methanol (20 mL) and the mixture stirred for 2 h (35–40 °C). Sodium hydroxide pellets (25 g) and toluene (80 mL) were added and the mixture heated at 65 °C (7·5 h). Water (130 mL) and toluene (40 mL) were added to the cooled mixture and the toluene phase extracted with 2 M hydrochloric acid. The acid extract was made alkaline to pH 11 with sodium hydroxide solution and extracted with toluene. The toluene was washed with brine, dried ($MgSO_4$) and evaporated to an oil (**3** and **9**) (13·6 g). The oil was chromatographed on silica gel G (deactivated with water) as a dry column. Elution with ethyl acetate afforded after crystallization from n-hexane the *N*-substituted morpholine (**9**) (2·1 g, 14%) m.p. 92–93 °C; (Found C 76·8; H, 8·2; N, 4·2, $C_{20}H_{25}NO_2$ requires C, 77·2; H, 8·0; N, 4·5%) δ ($CDCl_3$) 1·85 (m, 1 H), 2·32 (m, 3 H), 2·51 (m, 2 H), 2·75 (m, 4 H), 3·0 (m, 1 H), 3·70 (m, 4 H) and 7·17 (m, 10 H). *m/z* 311 (M^+). Further elution with ethyl acetate–ethanol–triethylamine (4:1:0·1) gave an oil (9·6 g) which was dissolved in diethyl ether and treated with ethanol saturated with hydrogen chloride. Crystallization of the precipitated hydrochloride from ethanol–ether gave (±)-2-benzylmorpholine hydrochloride (**3**) (8·0 g, 38%) m.p. 153–155 °C; (Found C, 61·4; H, 7·7; N, 6·3. $C_{11}H_{16}NOCl$ requires C, 61·8; H, 7·5; N, 6·5%). δ [$(CD_3)_2SO$] 3·40 (m, 9 H), 7·22 (m, 5 H) and 9·45 (m, 1 H). *m/z* 177 (M^+).

(+)- *and* (−)-*2-Benzylmorpholine hydrochlorides* (**3a** *and* **3b**). (±)-2-Benzylmorpholine (21·1 g) and (−)-dibenzoyltartaric acid (11·2 g) were heated under reflux in propan-2-ol (290 mL) (5 min) and allowed to cool over 18 h. The precipitate was collected and the filtrate retained (see below). Two crystallizations from 50% methanol/water gave the (−)-dibenzoyltartrate salt of **3b** as a colourless solid (11·0 g) m.p. 183–186 °C. The salt was added to excess of M sodium hydroxide solution and extracted with ethyl acetate. The ethyl acetate was washed with brine, dried ($MgSO_4$) and evaporated to an oil. Conversion to the hydrochloride salt as for the racemate **3** (above) gave (−)-2-benzylmorpholine hydrochloride **3b** after crystallization from propan-2-ol (3·3 g, 26%) m.p. 160–163 °C; (Found C, 61·5; H, 7·7; N, 6·1. $C_{11}H_{16}NOCl$ requires C, 61·8; H, 7·5; N, 6·5%). $[\alpha]_D^{25}$ −8·1° (c. 5·0 in 2 M HCl).

The original filtrate (see above) and (+)-dibenzoyltartaric acid (11·1 g) were heated under reflux (5 min) and allowed to cool over 18 h. The precipitate was collected and crystallized twice from 50% methanol–water to give, as a colourless solid, the (+)-dibenzoyltartrate salt **3a** (7·0 g) m.p. 184–186 °C. Conversion to the hydrochloride salt as previously described gave (+)-2-benzylmorpholine hydrochloride (**3a**) (2·2 g, 18%) m.p. 160–163 °C; (Found C, 61·6; H, 7·8; N, 6·3. $C_{11}H_{16}NOCl$ requires C, 61·8; H, 7·5; N, 6·5%). $[\alpha]_D^{25}$ +8·4° (c 5·0 in 2 M HCl).

The optical purity of the enantiomers **3a** and **3b** was determined by reaction during 18 h of each enantiomer with (+)-Moshers acid chloride (Dale 1969) in pyridine at room temperature. The reaction mixture was partitioned between water and ethyl acetate and the ethyl acetate phase dried ($MgSO_4$) and evaporated. The reaction mixture was chromatographed on a 5 μm Spherisorb silica HPLC column (250 × 4·6 mm) using a UV detector at 254 nm. The retention time for the (+)-diastereoisomer (**10a**) was 10 min and for **10b** 12 min.

Materials and methods

Diethylpropion hydrochloride (Sigma Chemical Co.) (**11**), (±)-2-benzylmorpholine (**3**) and its enantiomers (**3a** and **3b**) were examined as hydrochloride salts in all pharmacological tests.

Appetite suppressant tests. The appetite-suppressant activity was determined in mature beagle dogs trained to a 4 h feeding period daily, during which they had free access to meat. Groups of three dogs were dosed orally 1 h before their feeding period with 10 mg kg^{-1} of test compound in soft gelatine capsules. Food consumption was determined by weighing the food remaining at 1 h after the beginning of the feeding period. In the standard test all dogs received a placebo for 2 days, and then one group received drug while a parallel group received a placebo for a further 3 days. A comparison of the average food consumed on placebo days 1 and 2 of the test against that on drug-dosed days 3, 4 and 5 for the period 1 h after meat was made available, was expressed as a percentage reduction in food intake. Control animals were treated with the appetite suppressant diethylpropion (**11**).

A more precise definition of appetite suppressant potency was obtained from a modification of the above test involving four pairs of dogs. Dogs were allocated at random to one of three oral dosed treatment regimes of 2, 5 and 9 mg kg^{-1} and an undosed placebo pair of dogs. Drug was given in a capsule 1 h before free access to a meat meal on four successive days in a Latin Square design. Food consumed was recorded at 1, 2 and 4 h and results expressed as percentage reductions in food intake, from which an ED50 was derived for the 0–1, 0–2 and 0–4 h effects.

Tolerance test. The development of tolerance following repeated dosing of 2-benzylmorpholine (**3**) was studied in three dogs by extending the appetite suppressant test to 20 days of daily 10 mg kg^{-1} doses.

Stimulant tests. Stimulant behaviour in dogs was assessed by observation over 1 h following a 200 mg kg^{-1} oral dose of test compound or 5 mg kg^{-1} diethylpropion as control.

Results and discussion

The results displayed in Table 1 show the percentage reduction in meat consumed during the first hour after access to a meat meal by dogs previously dosed with 10 mg kg^{-1} p.o. of test compound. These results are compared with those for control animals dosed either with a placebo capsule or diethylpropion (**11**) as standard drug. The benzylmorpholine (**3**) showed a 53% reduction compared with 90% reduction for the standard drug (**11**) dosed at the lower level of 5 mg kg^{-1}. The smaller appetite

Table 1. Percentage reduction of food consumed by dogs 1 h after a meat meal.

Compound	Dose mg kg^{-1} p.o.	% Reduction 0–1 h
3	10	−53 ± 9·0
3a	10	−75 ± 9·5
3b	10	+3 ± 7·5
11	5	−90 ± 5·0
Placebo	—	+6 ± 9·0

suppressant effect found for the morpholine (**3**) compared with the standard drug (**11**) was, however, considered sufficient to predict clinical use in man provided that subsequent testing failed to reveal the attenuated stimulant properties characteristic of many clinically used appetite suppressants. In the acute test, using a Latin Square design, the morpholine (**3**) had an ED50 for the 0–1 h effect of 3 mg kg^{-1} compared to 2 mg kg^{-1} for the standard drug (**11**). A lower ED50 of 5·5 mg kg^{-1} for the 0–2 h effect of 2-benzylmorpholine (**3**) fell to an ED40 of 9 mg kg^{-1} for the 0–4 h effect.

Consideration of the enantiomers **3a** and **3b** showed that whereas the (+)-enantiomer (**3a**) caused a 75% fall in meat consumed after 1 h the corresponding (−)-enantiomer (**3b**) was without significant effect.

Dogs given oral doses of 200 mg kg^{-1} of the morpholine (**3**) were free of behavioural effects and stereotype actions. Under similar test conditions diethylpropion (**11**) caused overt stimulation at 5 mg kg^{-1} p.o.

An additional drawback in the use of appetite suppressants such as amphetamine (**1**) and phenmetrazine (**2**) is that they become less effective on repeated dosing. Thus a chronic dosing study involving 20 days oral dosing to three dogs at 10 mg kg^{-1} of the morpholine (**3**) was carried out. An average reduction of 75% in meat consumed at 1 h after meat was supplied on days 3, 4 and 5 declined to 35% by days 17–20 of the test.

Chronic dosing with the active (+)- enantiomer **3a** was not studied but it is unlikely that the presence of the inactive enantiomer **3b** in the racemate would have affected the outcome of the tolerance test.

In conclusion 2-benzylmorpholine (**3**) is a potent appetite suppressant agent in dogs when dosed orally. Resolution of the compound showed that appetite suppressant activity was confined to the dextrorotatory enantiomer (**3a**). In contrast to clinically used appetite suppressants of the central stimulant class, no stimulant or stereotype actions were seen for 2-benzylmorpholine (**3**). However, a chronic dosing study of morpholine (**3**) in dogs at its active dose level showed an unacceptable fall in the appetite suppressant effect indicating the development of tolerance.

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Phenytoin–bupropion interaction: effect on plasma phenytoin concentration in the rat

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Abstract—The effect of coadministration of bupropion (50 mg kg^{-1}, p.o.) on the disposition profile of phenytoin has been studied in the rat. Plasma phenytoin concentration was measured serially for 10 h by HPLC. Bupropion had little or no effect on the pharmacokinetic parameters of an acutely administered dose of phenytoin. Following multiple doses of phenytoin however (i.e. steady state) the coadministration of bupropion resulted in significant increases in the elimination half-life ($t_{\frac{1}{2}}$), the area under the plasma concentration-time curve (AUC) and the time to maximum plasma concentration (t_{max}). Allowing for the limitations of single dose studies, these results point to a possible pharmacokinetic interaction between bupropion and phenytoin—the clinical significance of which needs to be assessed.

Phenytoin is a primary anticonvulsant drug in the treatment of partial and generalized epilepsy with convulsive disorders. The drug has a narrow therapeutic range (10–20 μg mL^{-1}) and displays dose-dependent disposition kinetics around this range (Gugler et al 1976). Furthermore, its biotransformation has been shown to be markedly influenced by the concomittant use of other drugs (Kutt 1972; Perruca 1982). The antidepressants are one such group that would be coadministered with phenytoin for the treatment of depressed epileptic patients and in conditions such as post herpetic neuralgia (Raftery 1979).

Bupropion, a novel antidepressant drug has some common biotransformational features with phenytoin. It is both highly bound to plasma proteins (Findlay et al 1981) and extensively metabolized by hepatic microsomal enzymes (Schroeder 1983). Concomittant use of bupropion and phenytoin may thus present a potential for pharmacokinetic drug interaction.

The present study was designed to investigate any such interaction by studying the effect of a single dose of bupropion on the kinetics of a single/repeated dose of phenytoin in the rat.

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