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Synthesis and Analgetic Activity of *c*-3-Allyl(and 3-propyl)-1,3-dimethyl-4-phenylpiperidin-*r*-4-yl Propanoates

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Abstract

c-3-Allyl-1,3-dimethyl-4-phenylpiperidin-*r*-4-yl propanoate (1i) and the corresponding propyl derivative (1j) have been prepared and evaluated for analgetic activity. Compound (1i) shows very high potency which resides mostly in the (3*R*,4*R*)-enantiomer.

Introduction

Structure–activity relationships have been well established in strong analgetics derived from 1-methyl-4-phenylpiperidin-4-yl propanoate (1a) (for reviews see[1]). In particular, introduction of an equatorial 3-methyl group (1b) diminishes activity while the diastereomer (1c) shows enhanced activity.[2] However, the corresponding 3-propyl derivatives (1d) and (1e) are both less active than (1a).[3,4] From these and other results it has been suggested[1,4–6] that an equatorial 3-alkyl group interferes with receptor association but an axial 3-methyl group enhances receptor association by accommodation in a hydrophobic pocket of strictly limited size. This view is supported by a recent report[7] on the 3,3-dimethyl derivative (1f) which shows activity between that of (1a) and (1c). In the 3-allyl series,[3,4,8] however, the equatorial isomer (1g) is much more potent than (1a) or the diastereomer (1h). In this case a special subsidiary binding site for the double bond of the equatorial allyl group has been proposed.[1,4,8]

To further enhance activity in this series of compounds it seemed logical to combine the desirable features of an equatorial 3-allyl group and an axial 3-methyl group in the same molecule (1i). The preparation and analgetic activity of (1i) and the corresponding propyl derivative (1j), which should be much less active, are described in this communication.

[1] Casy, A. F., *Med. Res. Rev.*, 1982, **2**, 167; Portoghese, P. S., *Acc. Chem. Res.*, 1978, **11**, 21; Casy, A. F., *Prog. Drug Res.*, 1978, **22**, 149.
[2] Ziering, A., and Lee, J., *J. Org. Chem*, 1947, **12**, 911.
[3] Ziering, A., Motchane, A., and Lee, J., *J. Org. Chem.*, 1957, **22**, 1521.
[4] Bell, K. H., and Portoghese, P. S., *J. Med. Chem.*, 1973, **16**, 203.
[5] Larson, D. L., and Portoghese, P. S., *J. Med. Chem.*, 1973, **16**, 195.
[6] Portoghese, P. S., Gomaa, Z. S. D., Larson, D. L., and Shefter, E., *J. Med. Chem.*, 1973, **16**, 199.
[7] Ahmed, F. R., Laws, G. F., Madani, A. E., and Casy, A. F., *J. Med. Chem.*, 1985, **28**, 1947.
[8] Iorio, M. A., Damia, G., and Casy, A. F., *J. Med. Chem.*, 1973, **16**, 592.

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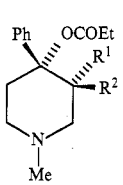
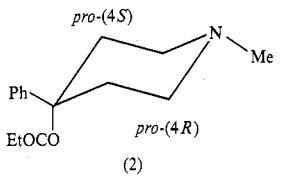
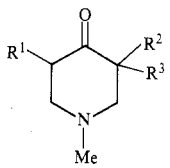
Further, in the 3-alkyl compounds (1a)–(1h) most of the activity resides in the enantiomer in which the alkyl group lies on the *pro*-(4*S*) side of the molecule[1,5–7,9,10] (see (2)). Thus, it was of interest to see if similar chiral discrimination would be observed in enantiomers of (1i).



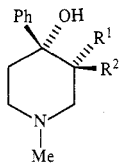
	R^1	R^2
(1a)	H	H
(1b)	Me	H
(1c)	H	Me
(1d)	Pr	H
(1e)	H	Pr
(1f)	Me	Me
(1g)	$CH_2{=}CHCH_2$	H
(1h)	H	$CH_2{=}CHCH_2$
(1i)	$CH_2{=}CHCH_2$	Me
(1j)	Pr	Me



(2)



	R^1	R^2	R^3
(3a)	H	Me	H
(3b)	H	H	H
(3c)	H	$CH_2{=}CHCH_2$	H
(3d)	H	$CH_2{=}CHCH_2$	Me
(3e)	$CH_2{=}CHCH_2$	H	Me



	R^1	R^2
(4a)	$CH_2{=}CHCH_2$	Me
(4b)	Me	$CH_2{=}CHCH_2$
(4c)	$CH_2{=}CHCH_2$	H
(4d)	H	$CH_2{=}CHCH_2$
(4e)	Pr	Me
(4f)	Pr	H
(4g)	H	Me

Results and Discussion

The ketone[11] (3a) needed for the synthesis of (1i,j) was prepared by the classic route involving conjugate addition of methylamine to methyl 2-methylpropenoate, a second addition of this product to methyl propenoate, Dieckmann cyclization to the β-keto ester followed by hydrolysis and decarboxylation. The 3-allyl group was introduced by the same procedure used to convert (3b) into (3c).[4] Thus, transacetalization of (3a) with 2,2-diallyloxypropane, acid-catalysed elimination of allyl alcohol to the allyl vinyl ether and Claisen rearrangement gave (3d) in 54% overall yield. The purified ketone (3d) (CH_3 singlet at δ 1·07 in the ^1H n.m.r. spectrum) was contaminated with about 5% of the isomer (3e) (CH_3 doublet at δ 0·93). Comparable predominance of the *gem*-disubstituted isomer has been observed in similar reactions on 2-substituted cyclohexanones.[12]

Reaction of (3d) with phenyllithium gave the predicted alcohol (4a). The diastereomer (4b) was not detected. Similar stereochemical results have been obtained

[9] Bell, K. H., and Portoghese, P. S., *J. Med. Chem.*, 1973, **16**, 589.
[10] Bell, K. H., and Portoghese, P. S., *J. Med. Chem.*, 1974, **17**, 129.
[11] Howton, D. R., *J. Org. Chem.*, 1945, **10**, 277.
[12] Lorette, N. B., and Howard, W. L., *J. Org. Chem.*, 1961, **26**, 3112.

with other piperidin-4-ones containing bulky 3-substituents.[3,13] A ^{1}H n.m.r. study[8] on the related (4c) and (4d) has shown that the signals due to the terminal methylene of the allyl group are relatively unaffected by protonation of the nitrogen in (4c) but are shifted downfield in (4d). In the case here the corresponding absorption suffered little change on protonation. This confirmed the equatorial nature of the allyl group in (4a).

Resolution of (4a) was effected with (2*R*,3*R*)- and (2*S*,3*S*)-2,3-dibenzoyloxysuccinic acids. Catalytic hydrogenation of the racemic and optically active allyl alcohols (4a) gave the corresponding propyl derivatives (4e).

The circular dichroism spectrum of the (−)-propyl derivative (4e) from (−)-(4a) showed positive Cotton effects in both the ^1L_b (*c.* 260 nm) and ^1L_a (*c.* 220 nm) bands.

Similar positive Cotton effects are shown by (3*R*,4*S*)-(4f)[14] and (3*S*,4*S*)-(4g).[15] On this basis the configuration of (−)-(4e) was assigned as (3*R*,4*R*) and hence that of (−)-4a) as (3*R*,4*R*). It should be noted that although both substituents in (−)-(4e) are located on the *pro*-(4*S*) side (see (2)) of the molecule in common with (3*R*,4*S*)-(4f) and (3*S*,4*S*)-(4g), the effect of disubstitution at C 3 is to change the priority order for substituents at C 4 which now becomes (*R*).

Racemic and optically active (4a) and racemic (4e) were converted into the corresponding propanoate esters (1i) and (1j) by treating with propanoyl chloride.

The esters were evaluated for analgetic activity in the standard mouse hot-plate test.[16] Racemic (1i) (ED_{50} 0·01 mg/kg) showed the expected increase in potency over those of racemic (1c) $(0·18)^2$ and (1g) (0·08).[4] Also, as expected, racemic (1j) showed an ED_{50} value (0·06 mg/kg) intermediate between those of (±-(1c) $(0·18)^2$ and (±)-(1d) (1·9).[4] Compound (1i) showed an extremely high enantiomeric potency ratio (3*S*,4*S*/3*R*,4*R* = 25/0·01 = 2500, compared to (1g) = 260).[9] This demonstrates that the methyl and allyl groups have strong receptor association when situated on the *pro*-(4*S*) side (as in (2)) of the molecule but sterically hinder association when on the *pro*-(4*R*) side.

Experimental

Infrared spectra were recorded with a Pye Unicam SP3-300 instrument; polystyrene lines were used for calibration. ^{1}H n.m.r. spectra were measured at 60 MHz with a Hitachi Perkin–Elmer R20 instrument; tetramethylsilane was used as internal reference. Mass spectra were recorded by Mr N. Keats with an A.E.I. MS 30 instrument. Optical rotations were measured with a Perkin–Elmer 241 spectropolarimeter in a 1-dm cell kept at 20°. Circular dichroism measurements were made with a Cary 60 instrument fitted with an O1 attachment; cell path lengths from 1·0 to 0·1 cm are used. Microanalyses were by the Australian Microanalytical Service.

1,3-Dimethylpiperidin-4-one (3a)

Methyl 2-methyl-3-(methylamino)propanoate, b.p. 37–42°/1·6 mm (lit.[11] 48·8–49·5°/8·5 mm), was obtained in 82% yield from methyl 2-methylpropenoate and methylamine as described. Further distillation of the crude product gave some (*c.* 10%) of the bis product, dimethyl 4-aza-2,4,6-trimethylheptanedioate, b.p. 92–104°/1·8 mm. The next addition to methyl propenoate gave dimethyl 2,4-dimethyl-4-azaheptanedioate in 91% yield, b.p. 94–97°/1·6 mm (lit.[11] 105–107°/4 mm). The procedure[11] for Dieckmann cyclization was modified by substituting

[13] Prostakov, N. S., and Gaivoronskaya, L. A., *Usp. Khim.*, 1978, **47**, 859.
[14] Bell, K. H., and Portoghese, P. S., unpublished data.
[15] Poupaert, J. H., and Portoghese, P. S., *Bull. Soc. Chim. Belg.*, 1977, **86**, 863.
[16] Eddy, N. B., and Leimbach, D., *J. Pharmacol. Exp. Ther.*, 1953, **107**, 385.

sodium hydride in dry benzene for metallic sodium.[17] The product was isolated as the hydrochloride, m.p. 187–188° (lit.[11] 188–191°), in 86% yield. Acid-catalysed hydrolysis and decarboxylation gave the ketone (3a) in 76% yield, b.p. 59–60°/8 mm (lit.[11] 43–43·4°/5·5 mm).

3-Allyl-1,3-dimethylpiperidin-4-one (3d)

This compound was synthesized by adapting the procedure[4] for the preparation of (3c). The intermediate diallyl acetal was not purified but was subjected directly to elimination and Claisen rearrangement. The ketone (3d) was obtained as a colourless oil in 54% yield, b.p. 54–56°/1·2 mm (Found: C, 72·1; H, 10·3; N, 8·4. $C_{10}H_{17}NO$ requires C, 71·8; H, 10·3; N, 8·4%). ν_{max}(neat) 1710 (C=O), 1642 (C=C) cm^{-1}. ^1H n.m.r. δ ($CDCl_3$) 0·93, d, $CHCH_3$ ((3e), 5%); 1·07, s, CCH_3; 1·80–3·20, broad envelope, CH_2, NCH_3; 4·97, 5·19, 5·75, all m, vinylic H. *m/z* 167 (M, 100%),

c*-3-Allyl-1,3-dimethyl-4-phenylpiperidin-*r*-4-ol (4a)*

A solution of ketone (3d) (12·0 g, 0·072 mol) in dry ether (100 ml) was added dropwise with stirring to ethereal phenyllithium (125 ml of 0·88 M, 0·11 mol). The temperature was maintained at 3–5° during the addition which was conducted under dry nitrogen. After complete addition, the mixture was stirred at room temperature for 18 h before decomposition by dropwise addition of water (25 ml). The aqueous phase was separated and extracted with additional ether (25 ml), then the combined ethereal solutions were washed with brine and dried ($MgSO_4$). Removal of the solvent left a pale yellow oil which crystallized on cooling. Recrystallization from light petroleum gave colourless crystals of the *alcohol* (4a) (13·4 g, 76%), m.p. 127–128° (Found: C, 78·5; H, 9·5; N, 5·5. $C_{16}H_{23}NO$ requires C, 78·3; H, 9·5; N, 5·7%). ν_{max} ($CHCl_3$) 3685, 3600 (broad) (OH), 1640 (C=C) cm^{-1}. ^1H n.m.r. δ ($CDCl_3$) 7·40, m, ArH; 5·07, bs, =CH; 2·15, s, NCH_3; 3·1–2·0, broad envelope, CH_2; 0·95, s, CCH_3. *m/z* 245 (M, 36%), 230 (M−CH_3, 10), 228 (M−OH, 13), 124 (27), 112 (26), 105 (29), 77 (31), 71 (30), 58 (40), 44 (100). T.l.c. (Eastman silica gel, ethyl acetate) of the filtrate from the recrystallization of (4a) showed some (4a) (R_F 0·2), a spot near the solvent front which may be some alkene resulting from elimination, and only traces of other components.

The *hydrochloride* (4a).HCl crystallized from ethanol/ether, m.p. 261–262° (Found: C, 68·4; H, 8·9; Cl, 12·7; N, 4·8. $C_{16}H_{24}ClNO$ requires C, 68·2; H, 8·6; Cl, 12·6; N, 5·0%). ^1H n.m.r. δ ($CDCl_3$) 7·30, m, ArH; 5·01, bs, =CH; 3·08, s, $^+NCH_3$; 0·88, s, CCH_3.

Resolution of (±)-(4a)

A mixture of racemic (4a) (3·5 g, 14 mmol) and (2*R*,3*R*)-(−)-2,3-dibenzoyloxysuccinic acid (5·4 g, 14 mmol) was dissolved in acetone (50 ml) at reflux. The solution was allowed to cool slowly then was left at room temperature for 5 days. The (−)-bis-amine (−)-acid salt was collected and washed with dry acetone. Yield 2·0 g (66%), m.p. 145–146°, $[\alpha]_D^{20}$ −25·2° (*c*, 1·00 in MeOH). Three further crystallizations from ethanol gave the *(−)-bis-amine salt*, m.p. 146–147°, of constant $[\alpha]_D^{20}$ −29·8° (*c*, 1·00 in MeOH) (Found: C, 69·2; H, 7·2; N, 3·1. $C_{50}H_{60}N_2O_{10}.H_2O$ requires C, 69·3; H, 7·1; N, 3·2%). ^1H n.m.r. δ (CF_3COOH) 7·80–6·30, m, ArH, 20H; 5·80, s, CHOCO, 2H; 0·60, s, CCH_3; 6H.

The (−)-base was liberated from an aqueous solution of the salt (1·4 g) by an excess of sodium hydroxide, then was extracted into ether, dried ($MgSO_4$), and the solvent was removed. Recrystallization of the residue from light petroleum gave *(3R,4R)-(−)-amine* (4a) (0·6 g, 76%), m.p. 115–116°, $[\alpha]_D^{20}$ −4·10° (*c*, 1·01 in $CHCl_3$) (Found: C, 78·1; H, 9·4; N, 5·5. $C_{16}H_{23}NO$ requires C, 78·3; H, 9·5; N, 5·7%).

The solvent was removed from the original acetone filtrate and the solid residue was treated with an excess of aqueous sodium hydroxide. The liberated sticky solid was then taken into ether, dried ($MgSO_4$), and the solvent was removed. Treatment of the residue with (2*S*,3*S*)-(+)-2,3-dibenzoyloxysuccinic acid (3·1 g) in acetone as before and recrystallization from ethanol gave the *(+)-bis-amine (+)-acid salt*, m.p. 146–146·5°, $[\alpha]_D^{20}$ +29·6° (*c*, 1·00 in MeOH) (Found: C, 69·5; H, 7·0; N, 3·1. $C_{50}H_{60}N_2O_{10}.H_2O$ requires C, 69·3; H, 7·1; N, 3·2%).

[17] McElvain, S. M., and Rorig, K., *J. Am. Chem. Soc.*, 1948, **70**, 1820.

From this salt was obtained the *(3S,4S)-(+)-amine* (4a), m.p. 115–116°, $[\alpha]_D^{20}$ +4·12° (*c*, 1·02 in $CHCl_3$) (Found: C, 78·1; H, 9·2; N, 5·5. $C_{16}H_{23}NO$ requires C, 78·3; H, 9·5; N, 5·7%).

*1,3-Dimethyl-4-phenyl-*c*-3-propylpiperidin-*r*-4-ol (4e)*

The allyl compound (4a) (1·0 g) in ethanol (25 ml) was added to a pre-reduced suspension of $PtO_2.H_2O$ (0·1 g) in ethanol (25 ml). Hydrogenation was conducted at room temperature and pressure until the theoretical uptake was complete (20 min). The catalyst was filtered off and the solvent was evaporated. Recrystallization of the residue from light petroleum gave the *alcohol* (4e) (0·91 g, 90%), m.p. 143–143·5° (Found: C, 78·0; H, 10·2; N, 5·6. $C_{16}H_{25}NO$ requires C, 77·7; H, 10·2; N, 5·7%). *m/z* 247 (M, 25%), 165 (16), 163 (17), 126 (33), 105 (25), 77 (25), 74 (42), 71 (38), 58 (73), 57 (33), 44 (100).

Similar hydrogenation of *(3R,4R)-(−)-(4a)* gave the *alcohol* *(3R,4R)-(−)-(4e)*, m.p. 112·5–113°, $[\alpha]_D^{20}$ −5·0° (*c*, 0·36 in $CHCl_3$) (Found: C, 77·9; H, 9·9; N, 5·9. $C_{16}H_{25}NO$ requires C, 77·7; H, 10·2; N, 5·7%). Circular dichroism (MeOH) (θ in degrees cm^2 $dmol^{-1}$) 267 (+112) 260 (+131), 254 (+75), *c.* 220 (*c.* +2400) nm.

Preparation of the Propionate Ester Hydrochlorides (1i).HCl and (1j).HCl

A mixture of alcohol (4a) (500 mg, 2 mmol), freshly distilled propanoyl chloride (0·4 ml, 5 mmol), and dry toluene (7 ml) was stirred at 100–110° under nitrogen for 5 h. The mixture was cooled to 0°, then the colourless crystals were collected, washed with dry toluene, ether, and dried. Recrystallization from ethyl acetate gave *c-3-allyl-1,3-dimethyl-4-phenylpiperidin-r-4-yl propanoate hydrochloride* (1i).HCl (0·4 g, 60%), m.p. 211–212° (Found: C, 67·7; H, 8·6; Cl, 10·9; N, 4·1. $C_{19}H_{28}ClNO_2$ requires C, 67·5; H, 8·4; Cl, 10·5; N, 4·2%).

Similarly alcohol (4e) gave 1,3-dimethyl-4-phenyl-*c*-3-propylpiperidin-*r*-4-yl propanoate hydrochloride (1j).HCl in 62% yield as colourless *crystals* from acetone, m.p. 230–231° (Found: C, 67·3; H, 8·4; Cl, 10·8; N, 4·2. $C_{19}H_{30}ClNO_2$ requires C, 67·1; H, 8·9; Cl, 10·4; N, 4·1%).

The enantiomeric forms of (1i).HCl were extremely hygroscopic and were purified by sublimation at 150–155°/0·01 mm. *(3S,4S)-(−)-(1i).HCl* from *(3S,4S)-(+)-(4a)* had m.p. 98–100°, $[\alpha]_D^{20}$ −0·4° (*c*, 0·21 in MeOH) (Found: C, 67·9; H, 8·7; Cl, 10·4; N, 4·2. $C_{19}H_{28}ClNO_2$ requires C, 67·5; H, 8·4; Cl, 10·5; N, 4·2%). *(3R,4R)-(+)-(1i).HCl*, from *(3R,4R)-(−)-(4a)*, had m.p. 98–101°. $[\alpha]_D^{20}$ +0·4° (*c*, 0·19 in MeOH) (Found: C, 67·6; H, 8·6; Cl, 10·8; N, 3·9. $C_{19}H_{28}ClNO_2$ requires C, 67·5; H, 8·4; Cl, 10·5; N, 4·2%).

Analgetic Testing

Preliminary evaluation of analgetic activity by the mouse hot-plate test[16] was carried out as described earlier.[18] More refined testing was done at the National Institutes of Health, Bethesda, MD, U.S.A. 20014, and those results are quoted in the discussion. Dependence liability of (1i) in monkeys was rated as high. Details of all the test results are available on request.*

Acknowledgment

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* From the Editor-in-Chief, Editorial and Publications Service, CSIRO, 314 Albert Street, East Melbourne, Vic. 3002.

[18] Bell, K. H., and Fullick, G., *Aust. J. Chem.*, 1985, **38**, 625.