Bridged Compounds as Potential Analgetics. Substituted 3-*exo*-Dimethylaminomethylnorbornanes as Potential Analgetics. Syntheses and Stereochemistry of Some 2-Hydroxy-2-aryl-substituted 3-*exo*-Dimethylaminomethylnorbornanes†

A. H. Beckett,* V. Nacci, and Abdul Q. Khokhar

Department of Pharmacy, Chelsea College, University of London, London, S.W.3. *Received July 30, 1971*

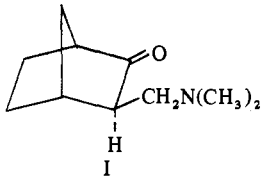
Diastereoisomers of 2-aryl-2-hydroxy-3-*exo*-dimethylaminomethylnorbornanes and their corresponding esters were prepared. Their configuration was established from ir spectra.

Molecules possessing significant analgetic activity require an aromatic group suitably orientated relative to a basic center; appropriately placed hydrocarbon projections can enhance or reduce this activity, depending upon their geometrical arrangement.[2] Analgetics may have rigid or nonrigid skeletons.

To determine the importance of distance between basic center and aryl function for analgetic action, and relative orientation of the groups, norbornane has now been used as the rigid framework to which the desired functional groups can be attached in a defined geometrical fashion with known distance between the groups.

A further aim was to produce stereoisomeric substrates suitable for the study of metabolic oxidative demethylation, since analgetics with the *N*-Me function are extensively demethylated in animals and man.[2,3]

Treatment of 3-exo-dimethylaminomethylnorbornan-2-one[4] (I) with excess PhLi gave a mixture of 2 isomeric alcohols, which were separated by crystallization. The isomer with mp 102° in 1% solution in CCl_4 showed a sharp peak at 3625 cm^{-1} (free OH) corresponding to structure IIa, in which intramolecular H bonding is sterically impossible (OH group is trans to the N atom), whereas the isomer with mp 72–74° showed an absorption maximum at 3325 cm^{-1} with a broad profile (bonded OH) and was assigned structure IIIa, in which the OH group is cis to N and intramolecular H bonding is possible.



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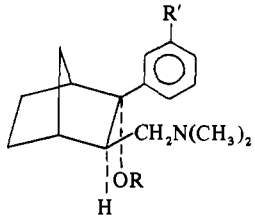
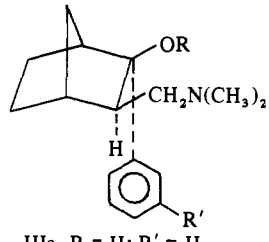


IIa, R = H; R′ = H
b, R = CH_3CO; R′ = H
c, R = H; R′ = CH_3O
d, R = CH_3CO; R′ = CH_3O



IIIa, R = H; R′ = H
b, R = CH_3CO; R′ = H
c, R = H; R′ = CH_3O
d, R = CH_3CO; R′ = CH_3O

Isomer IIa was obtained in greater yield, a result in agreement with the "rule of exo addition" to norbornan-2-one compounds with no syn 7-substituents,[5-7] *e.g.*, metal hydride reductions of norbornan-2-one[8] and 3-*exo*-dimethylaminomethylnorbornan-2-one.[9] Isomer IIa was also obtained as the main product when the PhLi addition was carried out at low temp.

Isomer IIIa was acetylated under milder conditions than IIa to give IIIb in better yield, since IIa possesses the more hindered OH group. Acetylation of IIa to IIb was achieved in good yield by heating it with isopropenyl acetate and TsOH.[10] Reduction of acetate IIIb with LAH gave the original alcohol (IIIa) showing that acetylation had proceeded with retention of configuration.

2-*m*-Anisyl-2-hydroxy-3-*exo*-dimethylaminomethylnorbornanes (IIc, IIIc) were prepared in a similar manner using *m*-anisyl Grignard reagent and stereochemical assignments were made from ir spectral data, *i.e.*, the compound exhibiting a sharp peak in 1% solutions of CCl_4 at 3600 cm^{-1} (free OH) was assigned the structure IIc, and to the compound which showed a broad absorption at 3270 cm^{-1} (bonded OH) the structure IIIc.

Acetylation of IIc and IIIc was achieved in reasonable yield by heating a mixture of the amino alcohol hydrochlorides, isopropenyl acetate, and TsOH.

Experimental Section‡

2-*endo*-Hydroxy-2-*exo*-phenyl-3-*exo*-dimethylaminomethylnorbornane (IIa) and 2-*exo*-Hydroxy-2-*endo*-phenyl-3-*exo*-dimethylaminomethylnorbornane (IIIa). To a soln of PhLi in dry Et_2O from 0.40 g (0.058 g-atom) of Li and 4.27 g (0.03 mole) of PhBr was added, with stirring under N_2, a soln of 4.1 g (0.0245 mole) of 3-*exo*-dimethylaminomethylnorbornan-2-one (I) in 15 ml of dry Et_2O at a rate sufficient to maintain reflux. The reaction mixt was heated under reflux for further 8 hr, cooled, and decompd by pouring onto crushed ice–HCl (1:1). The Et_2O layer was sepd and washed with dil HCl (10 ml), and the acid soln was returned to the reaction mixt. This was made basic with solid K_2CO_3 and extd with Et_2O, and the ext was dried (K_2CO_3). Removal of Et_2O under reduced pressure gave 5.45 g of crude oil which solidified on standing. This product was treated with a small amt of petr ether (bp 40–60°) and after standing overnight at 0°, the resulting white solid was washed with a little cold petr ether (bp 40–60°) to give 3.8 g of colorless cryst product (mp 96–98°). Recrystn from petr ether (bp 40–60°) gave 3.5 g (58%) of IIa as colorless prisms: mp 102°; $\nu_{max}^{CCl_4}$ 3625 cm^{-1} (free OH); ν_{max}^{Nujol} 3100 (OH), 705, 765 cm^{-1} (C_6H_5); nmr ($CDCl_3$) δ 1.9 (s, 1, OH), 2.0 (s, 6, $N(CH_3)_2$), 7.15–7.65 (m, 5, C_6H_5). *Anal.* ($C_{16}H_{23}NO$) C, H, N. The HCl salt melted at 190.5–192° dec (from EtOH–Et_2O).

The mother liquor remaining after filtration of IIa was decolorized with charcoal and after concg it to a small vol was allowed to cool. After 1 week the ppt was filtered and recrystd from petr ether

†A summary was published by Consiglio Nazionale Delle Richerche of a report read by one of us (V. Nacci) to the meeting of Chimica Del Farmaco e Dei Prodotti Biologicamente Attivi, Rome, December 15-18, 1969, p 53.1. Compounds IIa and IIIa have since been reported by Krieger and Arstila.[1]

‡All melting points were detd in a capillary tube on a Townson and Mercer block and are uncorrected. Ir spectra were recorded on a Unicam SP 200 and nmr spectra were detd in $CDCl_3$ (Me_4Si) on 60 MHz. Perkin-Elmer R-10 spectrometer. Hydroxyl nmr signals were located by exchange with D_2O. Where analyses are indicated only by symbols of the elements, analytical results obtained for those elements were within ±0.4% of theoretical values.

(bp 40–60°) to give 0.28 g (4.7%) of IIIa as colorless prisms: mp 72–74°; $\nu_{max}^{CCl_4}$ 3325 cm^{-1} (bonded OH); ν_{max}^{Nujol} 3275 (OH), 705, 745 cm^{-1} (C_6H_5); nmr δ 2.06 (s, 6, $N(CH_3)_2$), 5.1–5.6 (broad band, 1, OH), 7.1–7.7 (m, 5, C_6H_5). *Anal.* ($C_{16}H_{23}NO$) C, H, N. The HCl salt melted at 227° dec (from EtOH–Et_2O).

2-*endo*-Acetoxy-2-*exo*-phenyl-3-*exo*-dimethylaminomethylnorbornane (IIb). A mixt of 1.1 g (0.0046 mole) of IIa, 1.0 g of TsOH, and 20 ml of isopropenyl acetate was heated under reflux for 6 hr. The major part of the solvent was evapd under reduced pressure and to the residue were added H_2O (10 ml) and Et_2O (10 ml). The aqueous layer was sepd and made alkaline with solid K_2CO_3 with constant cooling; the free base was extd with Et_2O (3 × 10 ml). The combined exts were dried (K_2CO_3), and removal of Et_2O under reduced pressure gave a white solid (1.1 g, mp 100–105°). Recrystn from EtOH–H_2O gave 0.7 g (54%) of IIb as colorless needles: mp 108–110°; ν_{max}^{Nujol} 1730, 1240 cm^{-1} (CO); nmr δ 2 (s, 3, $COCH_3$), 2.04 (s, 6, $N(CH_3)_2$), 7.3 (m, 5, C_6H_5). *Anal.* ($C_{18}H_{25}NO_2$) C, H; N: calcd, 4.87; found, 5.38. The HCl salt melted at 118–120° (from Me_2CO–Et_2O). The same compd was obtd, but in lower yield, using the method described to prepared IIIb, but it was necessary to heat under reflux for 6 hr.

2-*exo*-Acetoxy-2-*endo*-phenyl-3-*exo*-dimethylaminomethylnorbornane (IIIb). A mixt of 1.0 g of 2-*exo*-hydroxy-2-*endo*-phenyl-3-*exo*-dimethylaminomethylnorbornane (IIIa), 0.5 g of anhyd AcONa, and 5 ml of Ac_2O was heated at 130° for 2 hr. After cooling, the reaction mixt was poured onto crushed ice (20 g). The soln was acidified with dil HCl (1:1) (2 ml), washed with Et_2O (2 × 10 ml), and made alkaline with solid K_2CO_3. The base was extd with Et_2O (3 × 10 ml), and the combined exts were dried (K_2CO_3). The solvent was removed under reduced pressure to give 1.1 g of colorless oil which solidified on standing overnight at 0°. Recrystn from EtOH–H_2O gave 0.7 g (63%) of IIIb as colorless prisms: mp 57–58°; ν_{max}^{Nujol} 1730, 1240 cm^{-1} (CO); nmr δ 1.94 (s, 3, $COCH_3$), 2.22 (s, 6, $N(CH_3)_2$), 7.1–7.65 (m, 5, C_6H_5). *Anal.* ($C_{18}H_{25}NO_2$) C, H, N. The HCl salt melted at 214–215° dec (from EtOH–Et_2O).

Reduction of IIIb with LAH. To a suspension of 0.1 g of LAH in 15 ml of dry Et_2O was added with stirring a soln of 0.17 g of IIIb in 5 ml of dry Et_2O. After heating the mixt under reflux overnight, it was decompd with ice. The filtrate was dried (K_2CO_3) and concd under reduced pressure to give 0.09 g of white solid, mp and mmp with IIIa 72–74° and ir spectrum identical with that of IIIa.

2-*endo*-Hydroxy-2-*exo*-*m*-anisyl-3-*exo*-dimethylaminomethylnorbornane (IIc) and 2-*exo*-Hydroxy-2-*endo*-*m*-anisyl-3-*exo*-dimethylaminomethylnorbornane (IIIc). A soln of 8.36 g (0.05 mole) of 3-*exo*-dimethylaminomethylnorbornan-2-one (**I**) in 50 ml of dry Et_2O was added under N_2 to a stirred soln of Grignard reagent in dry ether (100 ml) prepared from 1.82 g (0.075 g-atom) of Mg turnings and 14 g (0.075 mole) of *m*-bromoanisole at a rate sufficient to maintain reflux. The mixt was heated under reflux for 8 hr, cooled, and decompd by pouring onto crushed ice HCl (1:1). The layers were sepd and the aqueous layer was made alkaline with solid K_2CO_3. The liberated base was extd with $CHCl_3$ (6 × 50 ml) and the combined exts were dried (K_2CO_3). Removal of $CHCl_3$ under reduced pressure gave 13.2 g of crude oil, which was treated with a little petr ether (bp 40–60°) and scratched until a colorless solid sepd; the suspension was allowed to cool overnight. The solid was collected and washed with petr ether (bp 40–60°) to give 4.7 g of cryst product, mp 100–103°. Recrystn from PhH–petr ether (bp 40–60°) afforded 3.5 g (25.5%) of IIc as colorless prisms: mp 105–106.5°; $\nu_{max}^{CCl_4}$ 3600 cm^{-1} (free OH); ν_{max}^{Nujol} 3150 (OH), 710, 785, 1595, 1610 cm^{-1} (*m*-anisyl); nmr δ 2.01 (s, 6, $N(CH_3)_2$), 3.76 (s, 3, OCH_3), 6.96–7.36 (m, 4, *m*-anisyl). *Anal.* ($C_{17}H_{25}NO_2$) C, H, N. The HCl salt melted at 201–202° dec (from EtOH–Et_2O).

The mother liquor was decolorized with charcoal and evapd to dryness, and the residue (7.7 g of yellow oil) was dissolved in dry Et_2O (250 ml). A soln of EtOH–HCl (10%) was added dropwise with stirring until pptn was complete. The suspension of hydrochloride was filtered, washed with dry Et_2O, and quickly crystd from EtOH–Et_2O to give 4.1 g (26%) of IIIc·HCl: mp 178.5–181° dec. *Anal.* ($C_{17}H_{26}ClNO_2$) H, N, Cl; C: calcd, 65.47; found, 65.00. The HCl salt (4 g) was dissolved in H_2O (50 ml) and made alkaline with solid K_2CO_3. The base was extd with Et_2O (6 × 30 ml) and the combined exts were dried (K_2CO_3) and evapd under reduced pressure. Compd IIIc was obtd in quantitative yield as a colorless oil: $\nu_{max}^{CCl_4}$ 3270 cm^{-1} (bonded OH); ν_{max}^{Nujol} 3270 (OH), 703, 790, 1585, 1605 cm^{-1} (*m*-anisyl); nmr δ 2.07 (d, 6, $N(CH_3)_2$), 3.81 (s, 3, OCH_3) 7.05–7.46 (m, 4, *m*-anisyl).

2-*endo*-Acetoxy-2-*exo*-*m*-anisyl-3-*exo*-dimethylaminomethylnorbornane (IId). A mixt of 0.7 g (0.002 mole) of IIc·HCl, 50 mg of TsOH, and 20 ml of isopropenyl acetate was heated under reflux for 15 hr. The solvent was evapd under reduced pressure and the residue dissolved in H_2O (10 ml).

The aqueous soln was washed with Et_2O (2 × 5 ml) and made alkaline with solid K_2CO_3. The pptd oil was extd with Et_2O (3 × 10 ml) and the combined exts were decolorized with charcoal, dried (K_2CO_3), and evapd to give IId as a viscous light yellow oil (0.4 g, 57%): ν_{max}^{Nujol} 1240, 1735 cm^{-1} (CO); nmr (D_2O) of HCl salt δ 2.13 (s, 3, $COCH_3$), 2.27 (s, 6, $N(CH_3)_2$), 3.83 (s, 3, OCH_3), 6.95–7.45 (m, 4, *m*-anisyl). The oil was dissolved in EtOH (5 ml), and excess satd EtOH–picric acid was added. Recrystn from EtOH gave 0.36 g (30%) of IId·picrate as yellow prisms: mp 149–151° dec. *Anal.* ($2C_{19}H_{27}NO_3 \cdot 3C_6H_3N_3O_7$) C, H, N.

2-*exo*-Acetoxy-2-*endo*-*m*-anisyl-3-*exo*-dimethylaminomethylnorbornane (IIId). A mixt of 2.17 g (0.007 mole) of 2-*exo*-hydroxy-2-*endo*-*m*-anisyl-3-*exo*-dimethylaminomethylnorbornane·HCl (IIIc·HCl), 0.1 g of TsOH, and 60 ml of isopropenyl acetate was heated under reflux for 6 hr, and the residue was crystd from Me_2CO–Et_2O to give 0.6 g (25%) of IIId·HCl: mp 146–148° dec; ν_{max}^{Nujol} 1240, 1735 cm^{-1} (CO); nmr δ 2.03 (s, 3, $COCH_3$), 3 (s, 6, $N(CH_3)_2$), 3.88 (s, 3, OCH_3), 6.85–7.50 (m, 4, *m*-anisyl). *Anal.* ($C_{19}H_{28}ClNO_3$) C, H, N, Cl.

Pharmacological results were obtained by J. C. Le Douarec, Societé Francaise de Recherche Medicale, Science Union et Cie, 96 - Suresnes, France.

Analgetic Activity. The compds§ exhibited slight analgetic activity at 25 mg/kg but less than codeine in mice in a modified[11] hot plate test.[12] Ip injection of aqueous solns was used, and the response measured 30 min after injection. No differences were exhibited in the activities of the isomeric alcohols and esters.

Other Activities. In the rotating rod test,[13] alcohol IIIa and the ester IIIb at 50 mg/kg had about the same effect as codeine 30 min after ip injection. The compds are toxic with LD_{50} about 150 mg/kg ip.

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§ The ester, IIId, was not tested because it was too hygroscopic.