Journal of the Iranian Chemical Society, Vol. 3, No. 2, June 2006, pp. 191-208.

JOURNAL OF THE
Iranian
Chemical Society

Synthesis of Certain 1,7,7-Trimethyl-bicyclo[2.2.1]heptane Derivatives with Anticonvulsant, Hypoglycemic and Anti-inflammatory Potential

M.N. Aboul-Enein[a,*], A.A. EL-Azzouny[a], Y.A. Maklad[a], Y.S. Sokeirik[a] and H. Safwat[b]

[a]*Department of Medicinal and Pharmaceutical Chemistry, National Research Center, Dokki, Cairo, Egypt*

[b]*Pharmaceutical Chemistry Department, Faculty of Pharmacy, Cairo University*

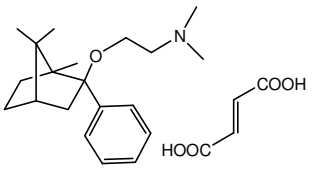
(Received 8 April 2006, Accepted 2 May 2006)

Starting from (1,7,7-trimethyl-bicyclo[2.2.1]hept-2-ylideneamino)-acetic acid methyl esters **6a, 6b**, the aryl esters of *exo*-2-[methyl-(1,7,7-trimethyl-bicyclo[2.2.1]hept-2-yl)-amino]-ethanol (**10a-f**) and *exo*-2-[methyl-(1,7,7-trimethyl-bicyclo[2.2.1]hept-2-yl)-amino-2-phenyl-ethanol (**10g-n**) are prepared. Also, from the reaction of 1,7,7-trimethyl-bicyclo[2.2.1]heptan nitramine **4** with either 2-amino-1-(4-nitrophenyl)-propane-1,3-diol (**17**) or 1-aminomethyl-cyclohexanol (**18**), the alcohol *exo*-1-[(1,7,7-trimethyl-bicylo[2.2.1]hept-2-ylamino)-methyl]-cyclohexanol (**13**), *exo*-1-(4-aminophenyl)-2-(1,7,7-trimethyl-bicyclo[2.2.1]hept-2-ylamino)-propane-1,3-diol (**14**) and 1-(4-aminophenyl)-2-[methyl-1,7,7-trimethylbicyclo[2.2.1]hept-2-yl]-amino]-propane-1,3-diol (**16**) are synthesized. At a dose level of 12.5 mg/kg, compounds **16** and **14** show a significant anticonvulsant protection against pentylenetetrazole seizures (100% and 83% protection, respectively) compared with diphenylhydantoin sodium (50 mg/kg, 100%) and deramciclane fumarate (25 mg/kg, 83%), used as reference drugs. Compound **10b** at dose level of 50 mg/kg displayed 41%, hypoglycemic activity, compared with gliclazide (10 mg/kg, 23%) as reference drug. Furthermore, the prepared compounds are screened for their anti-inflammatory potential at a dose level of 50 mg/kg. Compounds **10i**, **10g**, **14** and **10m** exhibited 92%, 90%, 88% and 80% inhibition in rat paw weight, respectively, with no sign of ulcerogenicity, compared with indomethecin (5 mg/kg, 81%).

Keywords: 1,7,7-Trimethlyl-bicyclo[2.2.1]heptane aminoalcohols, Esters, Anticonvulsants, Hypoglycemic and anti-inflammatory agents

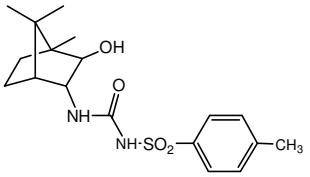
INTRODUCTION

A myriad of 1,7,7-trimethyl-bicyclo[2.2.1]heptane derivatives covers a great section of the medicinal chemistry armamentarium. These compounds display a broad spectrum of biological activities ranging from chemotherapeutic to pharmacodynamic agents [1-3]. Among these are anticonvulsant **I** [4,5], hypoglycemic **II** [6] and anti-inflammatory agents **III** [7], as diagrammed below.



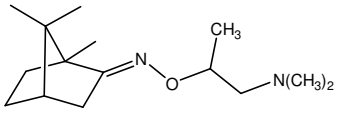
Deramciclane fumarate

I



Glibornuride (gutril (R))

II



III

*Corresponding author. E-mail: mnaboulenein@yahoo.com

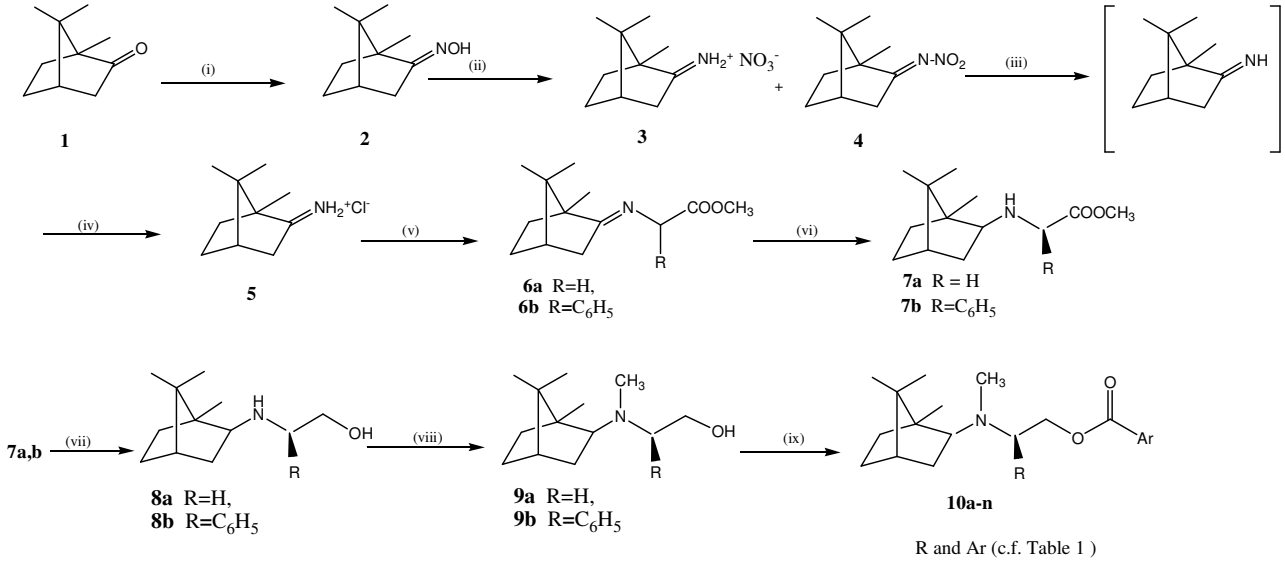
Accordingly, we embarked on a systematic investigation on the design and synthesis of certain 1,7,7 trimethylbicyclol [2.2.1]heptane derivatives **10a-n** (Scheme 1) and **13, 14** and **16** (Scheme 2) to be screened for their anticonvulsant, hypoglycemic and anti-inflammatory activities. Moreover, the potential for ulcerogenic effect is also studied.

EXPERIMENTAL

Chemistry

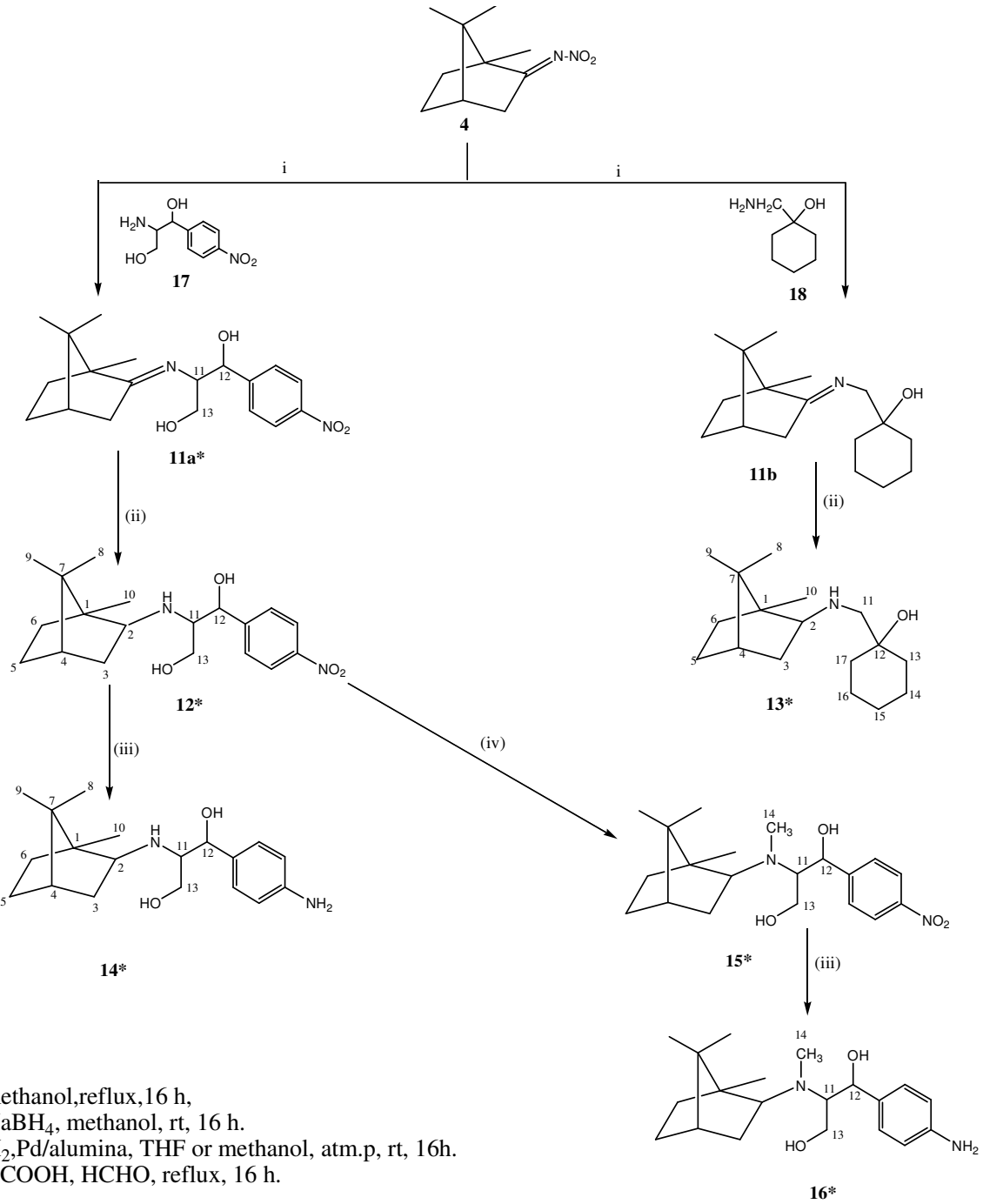
All melting points were determined with an electrothermal capillary melting point apparatus and were uncorrected. Infrared (IR) spectra were recorded as thin films (for oils) or as KBr pellets (for solids) with Jasco FTIR 300E and values are determined in cm^{-1}. ^1H NMR and ^{13}C NMR spectra were obtained on a Jeol EX 270 MHz instrument for the prepared compounds as bases in $CDCl_3$, using TMS as an internal standard. Chemical shift values were recorded in ppm δ scale: singlet (s), triplet (t), multiplet (m), broad (br). The mass spectra were obtained using a Finnigan Mat SSQ-7000 spectrometer, 70 eV, electron impact (EI). Elemental analyses were carried out at the Microanalytical Unit, National Research Center, Cairo. Single crystal X-ray crystallographic analyses were carried out on an Enraf Nonius FR 590 Kappa CCD 4 circles diffractometer. Column chromatography was performed on neutral alumina, activity grade I. The nomenclature is according to IUPAC rules.

1,7,7-Trimethyl-bicyclo[2.2.1]heptan imine nitrate (camphor imine nitrate), (3) and 1,7,7-trimethyl-bicyclo[2.2.1]heptan nitramine (camphor nitroimine), (4) Scheme 1. To a solution of 15 g (0.09 mol) of camphor oxime **2** in 150 ml of ether together with 35 ml of 20% H_2SO_4 contained in a separating funnel, 15 g (0.21 mol) of sodium nitrite in 25 ml of water was added dropwise. The separated deep red ether layer was allowed to stand until camphor imine nitrate **3** crystallized out as fine white needle-like crystals,



(i) $NH_2OH.HCl$, CH_3COONa, C_2H_5OH,H_2O, 60°C 15 h
(ii) $NaNO_2$,20% w/v H_2SO_4,ether
(iii) 30% aqeous NH_4OH, ether , r.t. , 24h
(iv) dry HCl gas , ether
(v) (a) 30% NH_4OH, ether ,r.t. 24 h.
(b) $RCH(NH_2)COOCH_3$ .HCl , ether, CH_2Cl_2, r.t., 72 h.
(vi) $NaBH_4$, CH_3OH, rt., 72 h..
(vii) $LiAlH_4$, ether, rt,18 h
(viii) HCOOH,HCHO, reflux, 16 h
(ix) Ar-COCl, TEA,DMP, dry benzene, reflux , 24h to achieve **10a-l:**
10f and **l** $\xrightarrow{x}$ **10m** and **n**
where x= H_2, Pd/alumina, THF, atm. P, r t.

Scheme 1



(i) methanol,reflux,16 h,
(ii) $NaBH_4$, methanol, rt, 16 h.
(iii) H_2,Pd/alumina, THF or methanol, atm.p, rt, 16h.
(iv) HCOOH, HCHO, reflux, 16 h.

*Carbon atoms are numbered in order to facilitate the assignment of their spectral data.(c.f. Table 2)

Scheme 2

m.p.: 158-9 °C. Filtration of the ether layer gave 3 g (20%) of **3**. The ether layer was then cautiously evaporated under reduced pressure to avoid decomposition of the thermolabile camphor nitroimine **4,** which was obtained as a greenish yellow oil, 10 g (71%).

1,7,7-Trimethyl-bicyclo[2.2.1]heptan-2-one imine hydrochloride, (5) Scheme 1. The ether solution from the above procedure containing both **3** and **4** was separated and shaken vigorously with 100 ml 30% aqueous NH_4OH, then allowed to stand overnight. The organic layer was separated, dried ($MgSO_4$), then treated with dry hydrogen chloride gas to give a solid white precipitate of **5**, which was filtered off to afford 8.5 g (90%) of 1,7,7-trimethyl-bicyclo[2.2.1]heptan imine hydrochloride (**5**), which is sublimable over 350 °C without melting.

General procedure for the preparation of (1,7,7-trimethyl-bicyclo[2.2.1]hept-2-ylideneamino)-acetic acid methyl ester (6a) and phenyl-(1,7,7-trimethyl-bicyclo[2.2.1]hept-2-ylideneamino)-acetic acid methyl ester (6b) Scheme 1. A solution of 9.4 g (0.05 mol) of **5** in 100 ml water was layered with 200 ml of diethyl ether and treated with 15 ml of 30% aqueous NH_4OH. The layers were equilibrated and then separated. The aqueous layer was extracted with ether (3 × 15 ml), the combined organic layers were collected, backwashed with water (2 × 20 ml), dried ($MgSO_4$), filtered and reduced in volume to 75 ml, then 0.05 mol of the corresponding α-amino acid methyl ester hydrochloride was added with 50 ml of dry methylene chloride. The suspension was stirred for 3 days, excluding moisture using a $CaCl_2$ guard tube. The formed precipitate of ammonium chloride was filtered off and the filtrate was cautiously concentrated under reduced pressure to give the crude product. The crude material was purified through flash chromatography (methylene chloride:methanol, 99:1) to give (1,7,7-trimethyl-bicyclo[2.2.1]hept-2-ylideneamino)-acetic acid methyl ester **6a** and phenyl-(1,7,7-trimethyl-bicyclo[2.2.1]hept-2-ylideneamino)-acetic acid methyl ester **6b** as pale yellow oils in a yields of 76 and 85%, respectively. For **6a** IR (liquid film): 1747 cm^{-1} (C=O) of ester and 1685 cm^{-1} (C=N); EI/MS, m/z (%): 223, M^+ (20%); 164, M-$COOCH_3^+$ (100). For **6b** IR (liquid film): 1741 cm^{-1} (C=O) of ester) and 1681 cm^{-1} (C=N); EI/MS, m/z (%): 299, M^- (4%); 240, M-$COOCH_3^+$ (100). Analysis, $C_{19}H_{25}NO_2$: calcd. C, 76.22; H, 8.42; N, 4.68; found: C, 76.35; H, 8.44; N, 4.71.

General procedure for the preparation of *exo*-(1,7,7-trimethyl-bicyclo[2.2.1]hept-2-ylamino)-acetic acid methyl ester (7a) , *exo*-phenyl-(1,7,7-trimethyl-bicyclo[2.2.1]hept-2-ylamino)-acetic acid methyl ester (7b). To a cold stirred solution of 0.05 mol of the esters **6a** or **6b** in 200 ml ethanol, 5.8 g (0.15 mol) of sodium borohydride was added at a rate such that the temperature of the reaction remained below 20 °C throughout the course of the addition. Upon complete addition of the borohydride, the reaction mixture was stirred at room temperature overnight. The solvent was removed under reduced pressure and the residue was dissolved in 150 ml of water. The aqueous phase was saturated with NaCl and extracted with ethyl acetate (3 × 50 ml). The combined organic extracts were dried over anhydrous $MgSO_4$, filtered and the solvent was removed under reduced pressure to give an oily residue. The residual substance was dissolved in 2 N HCl and the aqueous acidic layer was washed with ether (2 × 10 ml), rendered alkaline by 10% sodium carbonate and extracted with ethyl acetate (3 × 30 ml). The combined organic phases were dried ($MgSO_4$) and evaporated under reduced pressure to yield the amino esters **7a** and **7b** as pale yellow oils in 94 and 88% yields, respectively, which were used as such in the next experiment. For **7a**: IR (liquid film): 1740 cm^{-1} (C=O) of ester, disappearance of C=N band at 1685 cm^{-1}. For **7b**: IR (liquid film): 1741 cm^{-1} (C=O) of ester, disappearance of C=N band at 1681 cm^{-1}. EI/MS, m/z (%) 301, M^+ (2%); 242, M-$COOCH_3^+$ (100). Analysis, $C_{19}H_{27}NO_2$: calcd. C, 75.71; H, 9.03; N, 4.65; found: C, 75.73; H, 9.05; N, 4.66.

General procedure for the preparation of *exo*-2-(1,7,7-trimethyl-bicyclo[2.2.1]hept-2-ylamino)-ethanol (8a), *exo*-2-phenyl-2-(1,7,7-trimethyl-bicyclo[2.2.1]hept-2-ylamino)-ethanol (8b). To a suspension of 2 g (0.05 mol) of $LiAlH_4$ in 50 ml of dry ether, a solution of 0.025 mol of the corresponding amino ester **7a** or **7b** in 30 ml ether was added dropwisely, at a rate so to maintain gentle reflux of the reaction mixture.

Thereafter, stirring was continued overnight, the excess $LiAlH_4$ was decomposed by the cautious dropwise addition of 1.5 ml of saturated Na_2SO_4 followed by 8 ml NaOH (10%). After filtration of the formed granular white precipitate, the clear ether solution was dried ($MgSO_4$) and the free amino alcohol **8a** or **8b** was obtained, by removing the ether under

reduced pressure, as a yellow oil (98%). The hydrochloride salts of **8a** and **8b** were prepared using a methanolic-HCl solution.

For **8a**: m.p.: 286 ^{o}C HCl (isopropyl alcohol); IR (liquid film): 3391 cm^{-1} (stretching absorption of OH group); EI/MS, m/z (%): 197, M^{+} (35%). ^{1}H NMR ($CDCl_3$) δ (ppm): 0.78-1.8 (m, 16H, bornane protons except *H-2*); 2.52 (m, 1H, *H-2*); 2.78 (m, 2H, H-*12*); 2.8 (s, 1H, OH, disappear with D_2O); 3.56 (m, 2H, H-*13*); 3.69 (s, 1H, NH, disappear with D_2O). Analysis, $C_{12}H_{23}NO.HCl$: calcd. C, 61.65; H, 10.35; N, 5.99; found: C, 61.29; H, 10.15; N, 5.76.

For **8b**: mp.: 274 ^{o}C HCl (isopropyl alcohol); IR (liquid film): 3421 cm^{-1} (stretching absorption of OH group); EI/MS, m/z (%): 274, M+1^{-}(4%). ^{1}H NMR ($CDCl_3$) δ (ppm): 0.7-1.8 (m, 16H, bornane protons except H-*2*); 2.47 (m, 1H, H-*2*); 2.89 (s, 2H, NH, OH, disappear with D_2O); 3.46 (m, 1H, H-*12*); 3.62-3.82 (m, 2H, NH, H-*13*); 7.26-7.39 (m, 5H, aromatic). Analysis, $C_{18}H_{27}NO.HCl$: calcd. C, 69.77; H, 9.11; N, 4.52; found: C, 69.52; H, 8.97; N, 4.36.

***exo*-2-Methyl-(1,7,7-trimethyl-bicyclo[2.2.1]hept-2-yl)-amino]-ethanol (9a) and *exo*-2-[methyl-(1,7,7-trimethyl-bicyclo[2.2.1]hept-2-yl)-amino]-2-phenyl-ethanol (9b), Scheme 1 and Table 2.** The *exo*-amino alcohols **8a** or **8b** (0.03 mol) were refluxed while stirring with 1 ml (0.02 mol) of formic acid (100%) and 1.20 ml (0.015 mol) of formaldehyde (36%) for 16 h. The excess formic acid and formaldehyde solution was removed under reduced pressure. The residue was acidified with 2 N HCl and then washed with ether. The acidic layer was rendered alkaline with 10% sodium carbonate, extracted with ethyl acetate, dried ($MgSO_4$) and evaporated to afford, after column chromatography (n-heptane: ethyl acetate 9:1), **9a** and **9b** as yellow oils in 80% and 71% yields, respectively. For **9a**: analysis $C_{13}H_{25}NO$, calcd. C, 73.88; H, 11.92; N, 6.63; Found: C, 73.55; H, 11.63; N, 6.43. For **9b**: analysis $C_{19}H_{29}NO$, calcd. C, 79.39; H, 10.17; N, 4.87; found: C, 79.11; H, 10.05; N, 4.65.

General procedure for synthesis of aryl esters of *exo*-2-[methyl-(1,7,7-trimethyl-bicyclo[2.2.1]hept-2-yl)-amino]-ethanol (10a-f) and *exo*-2-[methyl-(1,7,7-trimethyl-bicyclo[2.2.1]hept-2-yl)-amino]-2-phenyl-ethanol (10g-l); Scheme 1, Table 1 and 2. To a stirred ice-cold solution of the amino alcohols **9a** or **9b** (0.01 mol), 1.5 ml (1.08 g, 0.015 mol) of triethylamine and 5 mg of 4-dimethylaminopyridine (DMAP) in dry benzene (20 ml), 0.012 mol of the corresponding acid chloride in 10 ml of dry benzene was added slowly. The mixture was stirred at room temperature for 1 h, refluxed for 18 h, and filtered. The filtrate was washed once with water (15 ml) and then with 10% $NaHCO_3$ (15 ml). The organic layer was evaporated under vacuum to afford a brown residue, which was dissolved in 2 N HCl, (15 ml), and washed with ether (3 × 10 ml). The aqueous acidic layer was basified with 10% sodium carbonate, extracted with ethyl acetate (3 × 20 ml), dried (Mg SO_4), filtered and evaporated under reduced pressure to afford the crude ester **10** as an oil. Purification by column chromatography (pet. ether:ethylacetate 9:1), gave the pure bases **10a-10l** as oils.

4-Amino-benzoic acid *exo*-2-[methyl-(1,7,7-trimethyl-bicyclo[2.2.1]hept-2-yl)-amino]-ethyl ester (10m) and 4-amino-benzoic acid *exo*-2-[methyl-(1,7,7-trimethyl-bicyclo [2.2.1]hept-2-yl)-amino]-2-phenyl-ethyl ester (10n); Scheme 1, Tables 1 and 2. A solution of 5 mmol of **10f** or **10l** in 40 ml tetrahydrofuran was hydrogenated at room temperature and atmospheric pressure, using 0.18 g of 10% palladium on alumina as a catalyst. After complete consumption of hydrogen, the catalyst was filtered off, and the solvent was removed *in vacuo*, to give the crude corresponding amino derivative 10m or 10n, respectively, as yellow oils, which were purified through column chromatography using n-heptane:ethyl acetate 8:2 to afford **10m** and **10n** in 92% and 95% yields, respectively. IR (liquid film) of **10m** and **10n**: 3369 cm^{-1} (NH_2 stretching), 1720-1727 cm^{-1} (C=O stretching), 1603-1664 cm^{-1} (NH_2 bending).

1-(4-Nitro-phenyl)-*exo*-2-(1,7,7-trimethyl-bicyclo[2.2.1] hept-2-ylideneamino)-propane-1,3-diol (11a), *exo*-1- [1,7,7-trimethyl-bicyclo [2.2.1] hept-2-ylideneamino)-methyl] cyclohexanol (11b), Scheme 2 and Table 2. In a round bottom flask containing a pre-dried 4 Å molecular sieve, was added 3.3 g (16.8 mmol) of 1,7,7-trimethyl-bicyclo[2.2.1]heptan nitramine (camphor nitroimine), **4,** dissolved in 15 ml methanol, followed by a solution of 15.3 mmol of the appropriate amino alcohols (**17** or **18**) in 15 ml methanol, then refluxed for 24 h. The reaction mixture was filtered and the filtrate was washed with chloroform (30 ml), saturated solution of $NaHCO_3$ (3 × 5 ml) followed by 5% NaCl (10 ml), and dried ($MgSO_4$). Then the solvent was removed under reduced pressure to give the crude products

11a and **11b** as viscous oils, which were purified by column chromatographs (pet ether: ethylacetate 9:1) to give pure **11a** and **11b** in 65% and 75% yields, respectively. IR (liquid film) of **11a** and **11b**: 3384, 3442 cm^{-1} (OH stretching) and at 1677-1645 cm^{-1} (C=N) respectively. For **11a**: analysis $C_{19}H_{27}N_2O$, calcd. C, 65.68; H, 7.83; N, 8.06; found: C, 65.59; H, 7.88; N, 8.11. For **11b**: analysis $C_{17}H_{29}NO$, calcd. C, 77.51; H, 11.10; N, 5.32; found: C, 77.60; H, 11.15; N, 5.38.

***exo*-1-(4-Nitro-phenyl)-2-(1,7,7-trimethyl-bicyclo[2.2.1] hept-2-ylamino)-propane-1,3-diol (12), *exo*-1-[(1,7,7-trimethyl-bicyclo[2.2.1]hept-2-ylamino)-methyl]-cyclohexanol (13), Scheme 2 and Table 2.** The imino alcohols **11a** and/or **11b** (0.05 mol) were dissolved in 200 ml methanol and cooled while stirring to -10 ^oC. Sodium borohydride (5.8 g, 0.15 mol) was added at such a rate to maintain the temperature of the reaction below 20 ^oC. The reaction mixture was stirred at room temperature overnight. The solvent was removed under reduced pressure, the residue was dissolved in saturated sodium chloride aqueous solution and extracted with ethyl acetate (3 × 50 ml). The combined organic extracts were dried, filtered and evaporated under reduced pressure to afford an oily product. The latter was dissolved in 2 N HCl and washed with ether (2 × 10 ml). The acidic layer was basified with 10% Na_2CO_3, extracted with ethyl acetate (3 × 30 ml), dried and evaporated under reduced pressure to achieve **12** and **13** as pale yellow oils in 77% and 75% yields, respectively, after being purified by column chromatography using pet. ether:ethyl acetate 8:2. For **12**: analysis $C_{19}H_{28}N_2O_4$, calcd. C, 65.49; H, 8.10; N, 8.04; found: C, 65.52; H, 7.15; N, 8.13. For **13**: analysis $C_{17}H_{31}NO$, calcd. C, 76.92; H, 11.77; N, 5.28; found: C, 76.83; H, 11.80; N, 5.29.

***exo*-1-(4-Amino-phenyl)-2-(1,7,7-trimethyl-bicyclo[2.2.1] hept-2-ylamino)-propane-1,3-diol (14), Scheme 2 and Table 2.** Compound **14** was prepared analogously to **10m** or **10n** using 1.65 g (0.005 mol) of **12**. After column chromatography purification using pet. ether:ethyl acetate 6:4, 1.4 g (85%) of compound **14** was obtained as a pale yellow oil. analysis $C_{19}H_{30}N_2O_2$: calcd. C, 71.66; H, 9.50; N, 8.80; found: C, 71.42; H, 9.32; N, 8.59.

***exo*-2-[Methyl-(1,7,7-trimethyl-bicyclo[2.2.1]hept-2-yl)-amino]-1-(4-nitro-phenyl)-propane-1,3-diol (15), Scheme 2 and Table 2.** Compound **15** was achieved by the same procedure adopted for **9a** or **9b** using 0.008 mol of **12**. After column chromatography purification using pet. ether:ethyl acetate 8:2, compound **15** was obtained as a yellow oil in 80% yield (2.3 g). Analysis $C_{20}H_{30}N_2O_4$: calcd. C, 60.27; H, 8.34; N, 7.73; found: C, 66.13; H, 8.36; N, 7.77.

1-(4-Amino-phenyl)-2-[methyl-(1,7,7-trimethyl-bicyclo [2.2.1]hept-2-yl)-amino]-propane-1,3-diol (16), Scheme 2 and Table 2. By using 1.8 g (5 mmol) of **15** dissolved in 40 ml of methanol, compound **16** was achieved (1.4 g, 85%). Analysis $C_{20}H_{32}N_2O_2$: calcd. C, 72.25; H, 9.70; N, 8.43; found: C, 72.39; H, 9.63; N, 8.31.

Pharmacology

Anticonvulsant activity. Anticonvulsant activity was adopted using the maximum pentylenetetrazole seizures test [8]. Experiments were carried out with groups of 6 mice each. The first group was divided into three subgroups and received intraperitoneally (i.p.) diphenylhydantoin and deramciclane fumarate as reference standards at different dose levels ranging from 12.5-50 mg/kg. The second group was divided into subgroups, each of which was injected (i.p.) with one of the tested compounds (in 7% tween-80) at graded doses (6-100 mg/kg). One hour later, pentylenetetrazole (90 mg/kg) was administered (i.p.).

Hypoglycemic activity. Groups of adult male albino rats (150 ± 20 g) of six animals each were fasted for about 18 h and thereafter, the animals were orally dosed with the test compound at a dose level of 50 mg/kg. One hour later, rats were sacrificed, blood was collected and plasma glucose levels were estimated using the glucose oxidase method [12]. Gliclazide (10 mg/kg) was employed as a reference drug against which the tested compounds were compared.

Anti-inflammatory activity. The inhibitory activity of the tested compounds (**10a-e, 10g-k, 10m-n** and **13, 14** and **16**) using the carrageenan-induced rat paw edema technique was determined according to the method of Winter *et al*. [9]. Rat paw edema was induced by subplanter injection of 0.05 ml of a 1% suspension of carrageenan in saline into the planter tissue of one hind paw. An equal volume of saline was injected into the other hind paw and served as a control. Four hours after administration of the compound, the animals were sacrificed and the paws were rapidly excised. The average weight of edema was estimated for the treated as well as the control and reference drug. The percentage inhibition of

weight of edema was evaluated [10]. Indomethacin (5 mg/kg) was employed as a reference standard against which the tested compounds were compared.

Ulcerogenic effect. Groups of adult male albino rats of six animals each (120-160 g) were fasted overnight, then orally given the tested compounds (50 mg/kg, body weight). Four hours later, the animals were sacrificed, their stomachs were removed, opened along the greater curvature, and the numbers of ulcers were assessed by adopting the method of Correll *et al* [11].

Statistical and data analysis. Data are expressed as means ± s.e.m. Statistical comparison between different groups was done using one way analysis of variance (ANOVA), followed by the multiple comparison test (post hoc LSD) [13]. Significance was accepted at $p < 0.05$.

RESULTS AND DISCUSSION

Chemistry

In Scheme 1, 1,7,7-trimethylbicyclo[2.2.1]heptan-2-one (D-camphor, **1**) was converted to its oxime **2** [14], which, through nitrosation, gave 1,7,7-trimethyl-bicyclo[2.2.1]-heptan imine nitrate (camphor imine nitrate, **3**) and 1,7,7-trimethyl-bicyclo [2.2.1]-heptan nitramine (camphor nitroimine, **4**). Subsequent ammonolysis of the formed mixture gave the unstable camphor imine, which was converted to its more stable hydrochloride salt **5**. Reaction of the latter with either glycine methylester hydrochloride or phenyl glycine methylester hydrochloride resulted in the corresponding imino esters **6a** and **6b**, respectively. Amino alcohols **8a** and **8b** were obtained by two successive reduction steps. Firstly, the reduction of the C=N group of compounds, **6a** and **6b,** using $NaBH_4$, which gave the same results when the reduction was performed with sodium cyanoborohydride [15], to exclusively afford the corresponding *exo*-N-bornylamino acid ester **7a** and **7b** in 94% and 85% yields, respectively [16,17]. Secondly, $LiAlH_4$ reduction of the ester grouping was performed to achieve the *exo* amino alcohols **8a** and **8b** [18].

These results were further confirmed through single crystal X-ray crystallographic analysis of the hydrochloride salts of both **8a** and **8b,** which proved that only the *exo* stereoisomers of **8** were formed (c.f. Figs. 1, 2). The amino alcohols **8a** and **8b** were N-methylated according to the Eschweiler-Clarke method [19] to produce the corresponding N-methyl alcohols, namely ***exo***-2-methyl-(1,7,7-trimethyl-bicyclo[2.2.1]hept-2-yl)-amino]-ethanol (**9a**) and ***exo***-2-[methyl-(1,7,7-trimethyl-bicyclo[2.2.1]hept-2-yl)-amino]-2-phenyl-ethanol (**9b**). Subsequent esterification with the appropriate acid chlorides gave the corresponding aryl esters **10a-n** (Table 1).

Their structures were confirmed through infrared spectra, which showed bands at 1714-1720 cm^{-1} (C=O, ester). Hydrogenation of the *p*-nitro esters **10f** and **10i** to their corresponding *p*-amino derivatives **10m** and **10n** was achieved using 10% Pd/alumina in THF under normal pressure and at room temperature.

The structure of compounds **9a, 9b** and **10a-n** were confirmed through ^1H, ^{13}C NMR and mass spectral data (c.f. Table 2). Scheme 2 illustrates the condensation of the highly electrophilic 1,7,7-trimethyl-bicyclo[2.2.1]heptan nitramine (camphor nitroimine) **4** with either D(-)-threo-2-amino-1-(4-nitrophenyl)-propan-1,3-diol (**17**) or 1-aminomethyl-cyclohexanol (**18**) in methanol to produce the respective imines **11a** and **11b** in 75% and 65% yields. Subsequent sodium borohydride reduction afforded the *exo* amino alcohols **12** and **13**, respectively. Their infrared spectra showed bands at 3397, 3442 cm^{-1} (OH groups) and the disappearance of the C=N bands at 1677 cm^{-1} and 1645 cm^{-1}, respectively. Catalytic hydrogenation of the nitro group of *exo* **12** gave *exo* **14** in 85% yield. Eschweiler-Clarke N-methylation of **12** led to **15,** which underwent catalytic hydrogenation to produce **16**. The structures were confirmed through ^1H, ^{13}C NMR and mass spectral data (c.f. Table 2).

Pharmacology

The aryl esters of both 2-[methyl-(1,7,7-trimethyl-bicyclo[2.2.1]hept-2-yl)-amino]-ethanol (R=H) **10a-e, 10m** and 2-[methyl-(1,7,7-trimethyl-bicyclo[2.2.1]hept-2-yl)-amino]-2-phenyl-ethanol (R = C_6H_5) **10g-k, 10n** are given the codes "Series A" and "Series B" respectively, while the N-bornanoamino alcohols **13, 14, 16** are given the code "Series C".

Anticonvulsant activity (Table 3). The data presented in Table 3 revealed that both the unsubstituted benzoate ester **10a** and the trimethoxybenzoate **10e** derivatives in "Series A" displayed 100% protection effect at a dose level of 100 mg/kg, which is similar to that of diphenylhydantoin (50 mg/kg) and

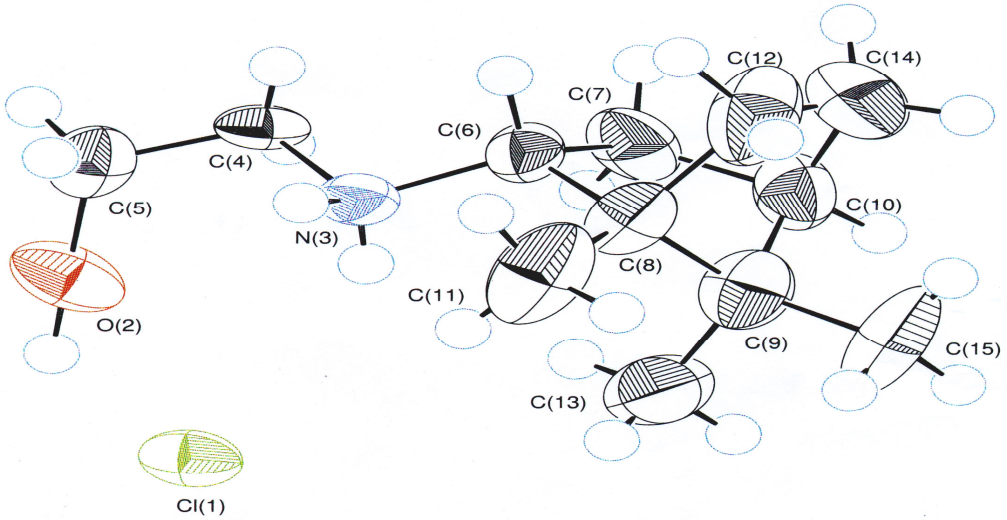


Fig. 1. Crystal analysis parameters of compound **8a**. Crystal data: Prism; z = 4, a = 13. 6353 Å, b = 7. 5051 Å, c = 14. 5192 Å, v = 1327.5, r = 0.100.

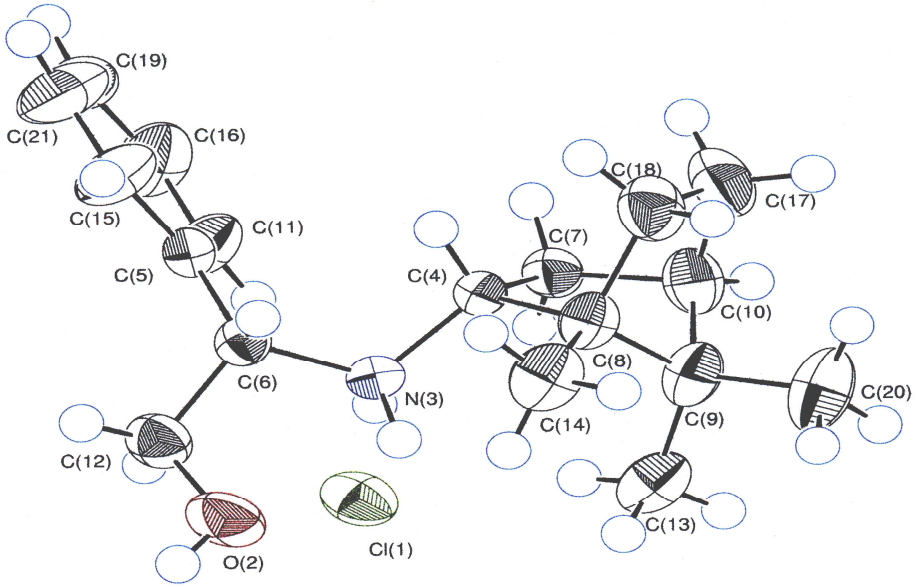
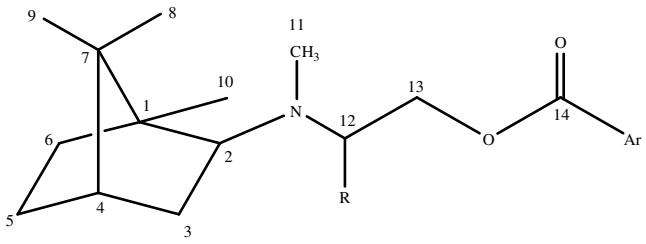


Fig. 2. Crystal analysis parameters of compound **8b**. Crystal data: Prism; z = 2, a = 7. 3678 Å, b = 10. 2253 Å, c = 12. 1462 Å, v = 886.04, r = 0.078.

Table 1. Physical and Analytical Data of Compounds **10a-n**



10a-n

No.[c]	R	Ar	Yield (%)	m.p. (°C)[a]	Formula (Mol. Wt.)	Analyses (%)			
							C	H	N
10a	H	C_6H_5	75	190-1	$C_{20}H_{29}NO_2$ .HCl	Calcd.	68.25	8.59	3.98
					351.98	F.	68.13	8.44	3.86
10b	H	4-Cl-C_6H_4	70	200-2	$C_{20}H_{28}ClNO_2$ .HCl	Calc.	62.17	7.57	3.63
					385.16	F.	61.95	7.45	3.46
10c	H	4-Br-C_6H_4	70	Oil[b]	$C_{20}H_{28}BrNO_2$	Calc.	60.91	7.16	3.55
					393.13	F.	59.65	7.06	3.45
10d	H	4-OCH_3-C_6H_4	65	175-7	$C_{21}H_{31}NO_3$ .HCl	Calc.	66.04	8.44	3.67
					381.21	F.	65.84	8.22	3.35
10e	H	3,4,5-$(OCH_3)_3$-C_6H_2	65	120-1	$C_{23}H_{35}NO_5$ .HCl	Calc.	62.50	8.21	3.17
					441.23	F.	62.13	7.99	3.01
10f	H	4-NO_2-C_6H_4	65	Oil[b]	$C_{20}H_{28}N_2O_4$	Calc.	66.64	7.83	7.77
					360.02	F.	66.24	7.63	7.59
10g	C_6H_5	C_6H_5	75	160-2	$C_{26}H_{33}NO_2$ .HCl	Calc.	72.96	8.01	3.27
					427.23	F.	72.59	7.82	3.15
10h	C_6H_5	4-Cl-C_6H_4	70	185-7	$C_{26}H_{32}ClNO_2$ .HCl	Calc.	67.53	7.19	3.03
					461.29	F.	67.23	6.95	2.95
10i	C_6H_5	4-Br-C_6H_4	70	180-1	$C_{26}H_{32}BrNO_2$ .HCl	Calc.	61.61	6.56	2.76
					505.19	F.	61.29	6.42	2.65
10j	C_6H_5	4-OCH_3-C_6H_4	75	150-1	$C_{27}H_{35}NO_3$ .HCl	Calc.	70.80	7.92	3.06
					457.28	F.	70.45	7.76	2.98
10k	C_6H_5	3,4,5-$(OCH_3)_3$-C_6H_2	74	193-4	$C_{29}H_{39}NO_5$ .HCl	Calc.	67.23	7.78	2.70
					517.26	F.	66.95	7.69	2.52
10l	C_6H_5	4-NO_2-C_6H_4	73	Oil[b]	$C_{26}H_{32}N_2O_4$	Calc.	71.53	7.39	6.42
					436.24	F.	71.34	7.25	6.29
10m	H	4-NH_2-C_6H_4	92	Oil[b]	$C_{20}H_{30}N_2O_2$	Calc.	72.69	9.15	8.48
					330.47	F.	72.44	8.97	8.36
10n	C_6H_5	4-NH_2-C_6H_4	95	Oil[b]	$C_{26}H_{34}N_2O_2$	Calc.	76.81	8.43	6.89
					406.26	F.	76.69	8.28	6.63

[a]Melting points of the corresponding hydrochloride salt. [b]Purified through column chromatography (c.f. experimental). [c]Carbon atoms are numbered in order to facilitate the assignment of ^1H and ^{13}C NMR data of **9a**, **9b** and **10a-n** (c.f. Scheme 1 and Table 2).

Table 2. Spectral Data of **9a, 9b, 10a-n, 11a, 11b, 12, 13, 14, 15** and **16**

	^{1}H NMR ($CDCl_3$) δ (ppm)	^{13}C NMR ($CDCl_3$) δ (ppm)	EI/ms, m/z (%)
9a	0.77-1.60 (m, 16H, bornane protons except H-*2*); 2.16 (br s, 1H, OH, which disappeared through deuteration with D_2O); 2.30 (s, 3H, H-*11*); 2.55 (t, 1H, H-*2*); 2.78 (t, 2H, H-*12*); 3.75 (t, 2H, H-*13*)	15.1 (C-*10*); 19.6 (C-*9*); 19.6 (C-*8*); 24.1 (C-*5*); 32.6 (C-*6*); 32.8 (C-*3*); 42.4 (C-*11*); 47.2 (C-*4*); 49.6 (C-*1*); 51.9 (C-*7*); 57.5 (C-*12*); 58.3 (C-*13*); 64.2 (C-*2*)	211, M^+, (75)
9b	0.81-1.62 (m, 16H, bornane protons except H-*2*); 2.13(br s, 1H, OH, which disappeared through denteration with D_2O); 2.29 (s, 3H, H-*11*); 2.44 (t, 1H, H-*2*); 3.95 (t, 2H, H-*13*); 3.99 (t, 1H, H-*12*); 7.10-7.29 (m, 5 aromatic protons))	15.1 (C-*10*); 19.8 (C-*9*); 19.9 (C-*8*); 23.9 (C-*5*); 32.5 (C-*6*); 32.8 (C-*3*); 39.8 (C-*11*); 47.1 (C-*4*); 52.2 (C-*1*); 52.4 (C-*7*); 61.9 (C-*2*); 63.2 (C-*13*); 66.6 (C-*12*); 127.4 (aromatic C-*4*); 128.6 (aromatic C-*3,5*); 128.9 (aromatic C-*2,6*); 138.2 (aromatic C-*1*)	288, MH^+, (100)
10a	0.96-1.58 (m, 16H, bornane protons except H-*2*); 2.27 (s, 3H, H-*11*); 2.45 (t, 1H, H-*2*); 2.63-2.89 (t, 2H, H-*12*); 4.38 (t, 2H, H-*13*); 7.31-7.98 (m, 5H aromatic protons)	15.1 (C-*10*); 19.8 (C-*9*); 19.9 (C-*8*); 23.8 (C-*5*); 32.3 (C-*6*); 32.7 (C-*3*); 40.2 (C-*11*); 47.1 (C-*4*); 51.9 (C-*1*); 52.3 (C-*7*); 55.1 (C-*12*); 61.9 (C-*13*); 63.9 (C-*2*); 128.8 (aromatic C-*3,5*); 129.9 (aromatic C-*2,6*); 130.8 (aromatic C-*1*); 133.2 (aromatic C-*4*); 166.7 (C-*14*, C=O)	315, M^+ (80), 244 (100)
10b	0.95-1.59 (m, 16H, bornane protons except H-*2*); 2.27 (s, 3H, H-*11*); 2.44 (t, 1H, H-*2*); 2.84 (t, 2H, H-*12*); 4.38 (t, 2H, H-*13*); 7.38-7.95 (AB System, 4H aromatic protons)	14.9 (C-*10*); 19.5 (C-*9*); 19.5 (C-*8*); 23.8 (C-*5*); 32.5 (C-*6*); 32.9 (C-*3*); 41.6 (C-*11*); 47.2 (C-*4*); 51.9 (C-*1*); 52.2 (C-*7*); 55.5 (C-*12*); 62.0 (C-*13*); 63.8 (C-*2*); 128.7 (aromatic C-*1*); 128.9 (aromatic C-*3,5*); 131.4 (aromatic C-*2,6*); 137.5 (aromatic C-*4*); 166.7 (C-*14*, C=O)	349, M^+ (100)
10c	0.96-1.59 (m, 16H, bornane protons except H-*2*); 2.27 (s, 3H, H-*11*); 2.44 (t, 1H, H-*2*); 2.82 (t, 2H, H-*12*); 4.36 (t, 2H, H-*13*); 7.55-7.89 (AB System, 4H aromatic protons)	15.0 (C-*10*); 19.5 (C-*9*); 19.5 (C-*8*); 23.7 (C-*5*); 32.4 (C-*6*); 32.6 (C-*3*); 41.8 (C-*11*); 47.2 (C-*4*); 51.9 (C-*1*); 52.3 (C-*7*); 55.4 (C-*12*); 62.2 (C-*13*); 63.9 (C-*2*); 129.3 (aromatic C-*1*); 131.5 (aromatic C-*3,5*); 132.2 (aromatic C-*2,6*); 127.0 (aromatic C-*4*); 166.7 (C-*14*, C=O)	393, M^+ (40); 180 (100)
10d	0.95-1.59 (m, 16H, bornane protons except H-*2*); 2.27 (s, 3H, H-*11*); 2.55 (t, 1H, H-*2*); 2.83 (t, 2H, H-*12*); 3.74 (s, 3H, O*CH$_3$*); 4.35 (t, 2H, H-*13*); 6.58-7.64 (AB System, 4H aromatic protons)	14.9 (C-*10*); 19.5 (C-*9*); 19.5 (C-*8*); 23.7 (C-*5*); 32.5 (C-*6*); 32.8 (C-*3*); 41.7 (C-*11*); 47.2 (C-*4*); 51.9 (C-*1*); 52.4 (C-*7*); 55.5 (C-*12*); 60.0 (O*CH$_3$*); 62.2 (C-*13*); 63.9 (C-*2*); 114.5 (aromatic C-*3,5*); 122.6 (aromatic C-*1*); 130.9 (aromatic C-*2,6*); 163.8 (aromatic C-*4*); 166.8 (C-*14*, C=O)	345, M^+ (60); 180 (100)

Table 2. Continued

10e	0.93-1.62 (m, 16H, bornane protons except H-*2*); 2.27 (s, 3H, H-*11*); 2.53 (t, 1H, H-*2*); 2.84 (t, 2H, H-*12*); 3.72 (S, 9H, 3,4,5 $(OCH_3)_3$); 4.34 (t, 2H, H-*13*); 6.69 (s, H aromatic protons)	15.0 (C-*10*); 19.5 (C-*9*); 19.5 (C-*8*); 23.4 (C-*5*); 31.8 (C-*6*); 31.9 (C-*3*); 41.8 (C-*11*); 47.0 (C-*4*); 51.8 (C-*1*); 52.3 (C-*7*); 55.1 (C-*12*); 56.3 (C-*3* and C-*5* of OCH_3 benzoate residue); 56.6 (C-*4* of OCH_3 benzoate residue); 62.1 (C-*13*); 107.2 (aromatic C-*2*, *6*); 124.3 (aromatic C-*1*); 144.0 (aromatic C-*4*); 150.2 (aromatic C-*3,5*); 166.8 (C-*14*, C=O)	405, M^+ (100)
10f	0.95-1.61 (m, 16H, bornane protons except H-*2*); 2.27 (s, 3H, H-*11*); 2.55 (t, 1H, H-*2*); 2.82 (t, 2H, H-*12*); 4.34 (t, 2H, H-*13*); 8.22-8.31 (AB System, 4H aromatic protons)	15.0 (C-*10*); 19.5 (C-*9*); 19.5 (C-*8*); 23.3 (C-*5*); 31.8 (C-*6*); 31.9 (C-*3*); 41.7 (C-*11*); 47.0 (C-*4*); 51.7 (C-*1*); 52.2 (C-*7*); 54.9 (C-*12*); 62.0 (C-*13*); 121.1 (aromatic C-*3,5*); 131.0 (aromatic C-*2,6*); 136.1 (aromatic C-*1*); 150.8 (aromatic C-*4*); 166.8 (C-*14*, C=O)	360, M^+ (84), 288 (100)
10g	0.93-1.60 (m, 16H, bornane protons except H-*2*); 2.27 (s, 3H, H-*11*); 2.55 (t, 1H, H-*2*); 4.32-4.45 (m, 1H, H-*12*); 4.61-4.76 (m, 2H, H-*13*); 7.21-7.89 (m, 10H, aromatic protons)	15.0 (C-*10*); 19.5 (C-*9*); 19.5 (C-*8*); 23.4 (C-*5*); 31.8 (C-*6*); 32.1 (C-*3*); 39.3 (C-*11*); 46.8 (C-*4*); 52.0 (C-*1*); 52.1 (C-*7*); 63.3 (C-*12*); 64.3 (C-*13*); 127.3 (aromatic C-*4*); 128.5 (aromatic C-*3,5*); 128.7 (benzoate C-*3,5*); 128.9 (aromatic C-*2,6*); 129.9 (benzoate C-*2,6*); 130.2 (benzoate C-*1*); 133.2 (benzoate C-*4*); 137.3 (aromatic C-*1*); 166.2 (C-*14*, C=O)	391, M^+ (7), 256 (100)
10h	0.94-1.60 (m, 16H, bornane protons except H-*2*); 2.27 (s, 3H, H-*11*); 2.55 (t, 1H, H-*2*); 4.33-4.45 (m, 1H, H-*12*); 4.62-4.76 (m, 2H, H-*13*); 7.07-7.21 (m, 5H, aromatic protons) 7.37-7.90 (AB System, 4H aromatic protons)	15.0 (C-*10*); 19.5 (C-*9*); 19.5 (C-*8*); 23.4 (C-*5*); 31.7 (C-*6*); 32.1 (C-*3*); 39.2 (C-*11*); 46.9 (C-*4*); 52.1 (C-*7*); 52.2 (C-*1*); 63.2 (C-*12*); 64.4 (C-*13*); 127.3 (aromatic C-*4*); 128.3 (4-chlorobenzoate C-*1*); 128.5 (aromatic C-*3,5*); 128.8 (4-chlorobenzoate C-*3,5*); 128.9 (aromatic C-*2,6*); 131.4 (4-chlorobenzoate C-*2,6*); 137.5 (aromatic C-*1*); 138.7 (aromatic C-*4*); 166.2 (C-*14*, C=O)	425, M^+ (14), 138 (100)
10i	0.93-1.61 (m, 16H, bornane protons except H-*2*); 2.27 (s, 3H, H-*11*); 2.55 (t, 1H, H-*2*); 4.36-4.50 (m, 1H, H-*12*); 4.63-4.76 (m, 2H, H-*13*); 7.12-7.22 (m, 5H, aromatic protons); 7.53-7.85 (AB System, 4H aromatic protons)	15.0 (C-*10*); 19.5 (C-*9*); 19.5 (C-*8*); 23.4 (C-*5*); 31.7 (C-*6*); 32.2 (C-*3*); 39.3 (C-*11*); 46.9 (C-*4*); 52.1 (C-*7*); 52.3 (C-*1*); 63.2 (C-*12*); 64.5 (C-*13*); 127.2 (aromatic C-*4*); 127.5 (4-bromobenzoate C-*4*); 128.5 (aromatic C-*3,5*); 128.9 (aromatic C-*2,6*); 129.3 (4-bromobenzoate C-*1*); 131.7 (4-bromobenzoate C-*3,5*); 132.2 (4-bromobenzoate C-*2,6*); 137.3 (aromatic C-*1*); 166.3 (C-*14*, C=O)	471, M^+ (100)

Table 2. Continued

10j	0.94-1.60 (m, 16H, bornane protons except H-*2*); 2.27 (s, 3H, H-*11*); 2.55 (t, 1H, H-*2*); 3.71 (s, 3H, OC*H*$_3$); 4.35-4.50 (m, 1H, H-*12*); 4.64-4.77 (m, 2H, H-*13*); 7.11-7.22 (m, 5H, aromatic protons); 6.87-7.85 (AB System, 4H aromatic protons)	15.0 (C-*10*); 19.5 (C-*9*); 19.5 (C-*8*); 23.3 (C-*5*); 31.6 (C-*6*); 32.1 (C-*3*); 39.2 (C-*11*); 46.9 (C-*4*); 52.1 (C-*7*); 52.2 (C-*1*); 55.8 (O*C*H$_3$); 63.3 (C-*12*); 64.5 (C-*13*); 114.3 (4-methoxybenzoate C-*3,5*); 127.3 (aromatic, C-*4*); 122.6(4-methoxybenzoate C-*1*); 128.4 (aromatic C-*3,5*); 128.9 (aromatic C-*2,6*); 131.1 (4-methoxybenzoate C-*2,6*); 137.5 (aromatic C-*1*); 164.4 (4-methoxybenzoate C-*4*); 166.2 (C-*14*, C=O)	421, M^+ (25), 256 (100)
10k	0.94-1.63 (m, 16H, bornane protons except H-*2*); 2.27 (s, 3H, H-*11*); 2.55 (t, 1H, H-*2*); 3.73 (s, 9H, (OC*H*$_3$)$_3$); 4.48-4.51 (m, 1H, H-*12*); 4.54-4.77 (m, 2H, H-*13*); 6.94-7.23 (m, 7H, aromatic protons)	15.0 (C-*10*); 19.5 (C-*9*); 19.5 (C-*8*); 23.3 (C-*5*); 31.7 (C-*6*); 32.2 (C-*3*); 39.2 (C-*11*); 46.9 (C-*4*); 52.2 (C-*1*); 52.2 (C-*7*); 56.2 (C-*3* of O*C*H$_3$ benzoate residue); 56.5 (C-*5* of O*C*H$_3$); 56.5 (C-4 of O*C*H$_3$ benzoate residue); 61.2 (C-*2*); 63.3 (C-*12*); 64.4 (C-*13*); 107.4 (C-*2,6* benzoate residue); 124.6 (C-*1* benzoate residue); 127.3 (aromatic C-*4*); 128.5 (aromatic C-*3,5*); 128.9 (aromatic C-*2,6*); 137.5 (aromatic C-*1*); 143.6 (C-*4* benzoate residue); 150.6 (C-*3,5* benzoate residue); 166.7 (C-*14*, C=O)	481, M^+ (36), 256 (100)
10l	0.95-1.64 (m, 16H, bornane protons except H-*2*); 2.27 (s, 3H, H-*11*); 2.55 (t, 1H, H-*2*); 4.37-4.50 (m, 1H, H-*12*); 4.62-4.76 (m, 2H, H-*13*); 7.09-7.22 (m, 5H, aromatic protons); 8.23-8.31(AB System, 4H aromatic protons)	15.0 (C-*10*); 19.5 (C-*9*); 19.5 (C-*8*); 23.3 (C-*5*); 31.6 (C-*6*); 32.2 (C-*3*); 39.1 (C-*11*); 46.8 (C-*4*); 52.1 (C-*1*); 52.1 (C-*7*); 61.3 (C-*2*); 63.2 (C-*12*); 64.3 (C-*13*); 121.1 (C-*3,5* benzoate residue); 127.2 (aromatic C-*4*); 128.5 (aromatic C-*3,5*); 128.9 (aromatic C-*2,6*); 130.8 (C-*2,6* benzoate residue); 136.2 (C-*1* benzoate residue); 137.3 (aromatic C-*1*); 152.6 (C-*4* benzoate residue); 166.7 (C-*14*, C=O)	436, M^+ (78), 256 (100)
10m	0.95-1.64 (m, 16H, bornane protons except H-*2*); 2.27 (s, 3H, H-*11*); 2.55 (t, 2H, H-*2*); 2.81 (t, 2H, H-12); 4.0 (br. s, 2H, NH_2 exchangeable with D_2O); 4.36 (t, 2H, H-*13*); 6.58-7.73 (AB System, 4H aromatic protons)	15.0 (C-*10*); 19.5 (C-*9*); 19.5 (C-*8*); 23.3 (C-*5*); 31.7 (C-*6*); 31.9 (C-*3*); 41.9 (C-*11*); 46.9 (C-*4*); 51.8 (C-*1*); 52.2 (C-*7*); 63.8 (C-*2*); 54.9 (C-*12*); 61.9 (C-*13*); 116.2 (aromatic C-*3,5*); 120.3 (aromatic C-*1*); 130.7 (aromatic C-*2,6*); 152.7 (aromatic C-*4*); 166.7 (C-*14*, C=O)	330, M^+ (100)

Table 2. Continued

10n	0.94-1.64 (m, 16H, bornane protons except H-*2*); 2.27 (s, 3H, H-*11*); 2.55 (t, 1H, H-*2*); 4.02 (br. S, 2H, NH_2 exchangeable with D_2O); 4.39-4.49 (m, 1H, H-*12*); 4.51-4.75 (m, 2H, H-*13*); 7.09-7.22 (m, 5H, aromatic protons); 6.56-7.71 (AB System, 4H aromatic protons)	15.0 (C-*10*); 19.5 (C-*9*); 19.5 (C-*8*); 23.2 (C-*5*); 31.7 (C-*6*); 32.1 (C-*3*); 39.2 (C-*11*); 46.9 (C-*4*); 52.2 (C-*1*); 52.2 (C-*7*); 61.2 (C-*2*); 63.2 (C-*12*); 64.4 (C-*13*); 116.3 (C-*3,5* benzoate residue); 120.2 (C-*1* benzoate residue); 127.2 (aromatic C-*4*); 128.5 (aromatic C-*3,5*); 128.9 (aromatic C-*2,6*); 130.6 (C-*2,6* benzoate residue); 137.5 (aromatic C-*1*); 152.6 (C-*4* benzoate residue); 166.7 (C-*14*, C=O)	406, M^+ (5); 134 (100)
11a	0.99-2.37 (m, 16H, bornane protons), one H of H-*11* and two OH protons which are exchangeable with D_2O; 3.41-3.68 (m, 2H, H-*13*); 4.48 (d, 1H, H-*12*); -7.46-8.13 (AB System, 4H aromatic protons)	6.1 (C-*10*); 19.6 (C-*9*); 19.6 (C-*8*); 28.6 (C-*5*); 32.0 (C-*6*); 36.1 (C-*3*); 46.9 (C-*4*); 51.4 (C-*7*); 54.4 (C-*1*); 61.6 (C-*13*); 63.6 (C-*11*); 77.8 (C-*12*); 121.0 (aromatic C-*3,5*); 129.0 (aromatic C-*2,6*); 144.6 (aromatic C-*1*); 145.7 (aromatic C-*4*); 184.7 (C-*2*).	347, MH^+ (100)
11b	0.99-2.38 (m, 16H, of bornane protons), 10 H of cyclohexane protons, two H of H-*11* and one O*H* proton, which is exchangeable with D_2O)	16.1 (C-*10*); 19.3 (C-*14* and C-*16);* 19.6 (C-*9*); 19.6 (C-*8*); 28.6 and 28.7 (C-*15* and C-*5);* 32.1 (C-*6*); 35.7 (C-*3*); 39.2 (C-*13* and C-*17*); 46.8 (C-*4*); 51.4 (C-*7*); 52.7 (C-*11*); 54.0 (C-*1*); 68.1 (C-*12*); 184.7 (C-*2*)	263, M^+ (100)
12	1.00-2.10 (m, 16H, of bornane protons), one H of N*H* and two O*H* protons, which are exchangeable with D_2O; 2.53-2.55 (m, 1H, H-*2*); 3.15-3.17 (m, 1H, H-*11*); 3.47-3.72 (m, 2H, H-*13*); 4.72 (d, 1H, H-*12);* 7.45-8.12 (AB System, 4H aromatic protons)	14.8 (C-*10*); 19.6 (C-*9*); 19.6 (C-*8*); 23.3 (C-*5*); 31.4 (C-*6*); 34.6 (C-*3*); 46.5 (C-*4*); 51.7 (C-*7*); 54.5 (C-*1*); 58.2 (C-*2*); 60.4 (C-*13*); 63.3 (C-*11*); 71.7 (C-*12*); 121.1 (aromatic C-*3,5*); 129.0 (aromatic C-*2,6*); 144.6 (aromatic C-*1*); 145.6 (aromatic C-*4*)	349, MH^+ (3); 196 (100)
13	0.99-1.68 (m, 16H, bornane protons) and 10H of cyclohexane protons; 2.00 (br. s, two protons of N*H* and O*H*) which are exchangeable with D_2O; 2.56-2.67 (m, 3H, H-*2* and H-*11*)	14.9 (C-*10*); 19.3 (C-*14* and C-*16*); 19.6 (C-*9*); 19.6 (C-*8*); 23.4 (C-*5*); 28.7 (C-*15*); 31.5 (C-*6*); 34.4 (C-*3*); 39.2 (C-*13* and C-*17*); 46.7 (C-*4*); 51.8 (C-*7*); 54.4 (C-*1*); 58.9 (C-*11*); 60.7 (C-*2*); 72.6 (C-*12*)	265, M^+ (100)
14	0.99-2.00 (m, 16H, bornane protons) and one H of N*H* and two *OH* protons, which are exchangeable with D_2O; 2.53-2.55 (m, 1H, H-*2*); 3.16-3.18 (m, 1H, H-*11*); 3.47-3.72 (m, 2H, H-*13*); 4.06 (br. s, 2H, NH_2 which are exchangeable with D_2O); 4.73 (d, 1H, H-*12*); 6.38-6.95 (AB system, 4H aromatic protons)	14.8 (C-*10*); 19.5 (C-*9*); 19.5 (C-*8*); 23.2 (C-*5*); 31.3 (C-*6*); 34.5 (C-*3*); 46.5 (C-*4*); 51.8 (C-*7*); 54.6 (C-*1*); 58.2 (C-*2*); 60.5 (C-*13*); 63.4 (C-*11*); 71.8 (C-*12*); 116.5 (aromatic C-*3,5*); 128.5 (aromatic C-*1*); 129.5 (aromatic C-*2,6*); 145.7 (aromatic C-*4*)	317, M^+-1 (15); 196 (100)

Table 2. Continued

15	0.99-2.00 (m, 16H, bornane protons) and two O*H* protons, which are exchangeable with D_2O; 2.26 (s, 3H, H-*14*); 2.52-2.54 (m, 1H, H-*2*); 3.16-3.17 (m, 1H, H-*11*); 3.46-3.71 (m, 2H, H-*13*); 4.73 (d, 1H, H-*12*); 7.44-8.11 (AB System, 4H aromatic protons)	14.9 (C-*10*); 19.5 (C-*9*); 19.5 (C-*8*); 23.3 (C-*5*); 31.7 (C-*6*); 32.3 (C-*3*); 40.1 (C-*14*); 46.8 (C-*4*); 52.0 (C-*7*); 52.2 (C-*1*); 58.0 (C-*13*); 62.1 (C-*2*); 68.1 (C-*11*); 69.4 (C-*12*); 121.1 (aromatic C-*3,5*); 129.1 (aromatic C-*2,6*); 144.6 (aromatic C-*1*); 145.7 (aromatic C-*4*)	361, M^+-1 (85); 210 (100)
16	0.99-2.05 (m, 16H, bornane protons); and two O*H* protons, which are exchangeable with D_2O; 2.26 (s, 3H, H-*14*); 2.52-2.54 (m, 1H, H-*2*); 3.16-3.18 (m, 1H, H-*11*); 3.46-3.71 (m, 2H, H-*13*); 4.05 (br. s, 2H, NH_2, which are exchangeable with D_2O); 4.72 (d, 1H, H-*12*); 6.39-6.95 (AB System, 4H aromatic protons)	14.9 (C-*10*); 19.4 (C-*9*); 19.4 (C-*8*); 23.2 (C-*5*); 31.7 (C-*6*); 32.2 (C-*3*); 40.2 (C-*14*); 46.9 (C-*4*); 52.2 (C-*7*); 52.2 (C-*1*); 57.9 (C-*13*); 67.9 (C-*11*); 69.4 (C-*12*); 116.5 (aromatic C-*3,5*); 128.6 (aromatic C-*1*); 129.2 (aromatic C-*2,6*); 145.8 (aromatic C-*4*)	333, M^+ (100)

Table 3. Anticonvulsant Potential of the Most Potent Compounds among Series A, B and C against Pentylenetetrazole-induced Seizures in Adult Male Albino Mice

Compd. No.[c]	Dose (mg/kg)	No. of[a] survival	Protection (%)
Control	-	0	0
Diphenyl-hydantoin	15	3	50
	25	4	67.67
	50	6	100
Deramciclane fumarate	12.5	3	50
	25	5	83.33
Series A			
10a[b]	50	2	33.33
	100	6	100
10b	25	1	16.67
	50	5	83.33
10c	50	0	0
	100	5	83.33
10d	20	0	0
	60	3	50
10e[b]	50	2	33.33
	100	6	100
10m	25	1	16.67
	50	3	50
Series B			
10g	25	1	16.67
	60	4	66.67
10h	25	2	33.33
	60	6	100
10i[d]	25	0	0
	60	0	0
10j[b]	25	2	33.33
	50	6	100
10k	50	1	16.67
	100	1	16.67
10n	25	2	33.33
	50	4	66.67
Series C			
13	6	3	50
	12.5	4	66.67
14	6	3	50
	12.5	5	83.33
16[b]	6	3	50
	12.5	6	100

[a]Out of six animals. [b]The most active compounds in each series. [c]Compounds **10 f** and **10 l** untested. [d]Inactive.

nearly effective as deramciclane fumarate (25 mg/kg) as reference standards.

On the other hand, in "Series B", both the *p*-methoxy as well as the *p*-chloro benzoate derivatives **10j** (50 mg/kg) and **10h** (60 mg/kg) displayed 100% protection effect. This effect was equipotent to that of diphenylhydantoin sodium (50 mg/kg) and nearly similar to deramciclane fumarate (25 mg/kg) used as reference drugs. Furthermore, the *p*-methoxybenzoate **10j** and the *p*-chlorobenzoate **10h** showed the same effect at a dose level of 60 mg/kg. The anticonvulsant activity in "Series A and B" had the following order of potency **10j > 10h > 10a = 10e > 10b > 10c > 10n > 10g > 10d > 10m > 10k.** Accordingly, this reveals that the anticonvulsant profile is augmented by the introduction of the phenyl moiety at position *2* in the ethanol scaffold.

Concerning "Series C", compound 1-(4-amino-phenyl)-2-[methyl-(1,7,7,-trimethyl-bicyclo[2.2.1]-hept-2-yl)-amino]-propane-1,3-diol (**16**) was found to be the most potent of the series. It showed a 100% protection effect at a dose level of 12.5 mg/kg compared with diphenylhydantoin sodium (50 mg/kg) as a reference standard drug, whereas, its N-dimethyl analogue **14** (12.5 mg/kg) exhibited equipotent protection activity (83%) as that of the reference standard deramciclane fumarate (25 mg/kg). Compounds of "Series C" showed

Table 4. Hypoglycemic Activity of Compounds **10a-n**[a], **13**, **14** and **16** (50 mg/kg) in Adult Male Albino Rats

Compd. No.[f]	Plasma glucose level (mg/dl)[d]	Change with respect to control value (%)
Control	84.86 ± 0.83	-
Gliclazide (10 mg/kg)	65.52 ± 1.07[b]	22.79
Series A		
10a	81.93 ± 1.03[a, c]	03.45
10b[e]	50.03 ± 0.74[b,c]	41.04
10c	81.07 ± 0.38[a, c]	04.47
10d	65.39 ± 1.07[b]	22.94
10e	70.96 ± 0.60[b, c]	16.38
10m	81.24 ± 0.55[a,c]	04.27
Series B		
10g	83.51 ± 0.54[c]	01.59
10h[e]	72.66 ± 0.68[b, c]	14.38
10i	75.59 ± 0.39[b, c]	10.92
10j	83.79 ± 0.77[c]	01.26
10k	84.43 ± 1.02[c]	00.51
10n	81.90 ± 0.69[a, c]	03.49
Series C		
13	83.99 ± 1.02[c]	01.03
14	80.73 ± 0.70[a, c]	04.87
16	81.73 ± 0.44[a, c]	03.69

[a]Except **f & l**. [b]$p < 0.01$ compared with control value. [c]$p < 0.01$ compared with gliclazide (10 mg/kg) value. [d]Each value represents the mean plasma glucose level (mg/dl) ±. s.e.m. of the number of animals in each group (n = 6). [e]represent the most active compound(s) in each series. [f]Compounds **10f** and **10l** untested.

decreasing anticonvulsant activity in the following order **16 > 14 > 13.**

Hypoglycemic effect (Table 4). In "Series A", the *p*-chlorobenzoate ester **10b** exhibited the highest reduction in blood glucose level (41%), compared with its phenyl congener **10h** (14%), in "Series B", with respect to control value, at a dose level of 50 mg/kg. Moreover, the ester **10b** showed 23.6% significant reduction in blood glucose level with respect to gliclazide (10 mg/kg).

In "Series A", the esters **10d** and **10e,** having the 4-methoxy-and 3,4,5-trimethoxy substitutions in the aromatic ring, induced 23% and 16% reduction in blood glucose level, respectively. This causes speculation that the hypoglycemic profile is decreased by the introduction of the phenyl moiety at position 2 in the ethanol scaffold. The hypoglycemic activity of the hypoglycemic activity of the other tested compounds showed weak effect.

Anti-inflammatory activity (Table 5). All the synthesized compounds (except **10f** and **10i**), as well as indomethacin as a reference drug, were tested at dose levels of 50 and 5 mg/kg, respectively.

In "Series A" where the 2-position in the ethanol scaffold

Table 5. Antiinflammatory Activity of Compounds **10a-n**, **13**, **14** and **16** (50 mg/kg) Using the Carrageenan-induced Rat Paw Edema Method

Compd. No[g]	Antiinflammatory activity	
	% Increase in weight[d] of paw edema (g) x ± s.e.m.	Inhibition (%)
Control	62.24 ± 2.68	-
Indomethacin (5 mg/kg)	11.79 ± 0.97[a]	81.06
Series A		
10a	35.38 ± 1.40[a, c]	43.16
10b	27.35 ± 1.33[a, c]	56.06
10c	32.79 ± 0.99[a, c]	47.32
10d	44.54 ± 1.21[a,c]	27.86
10e	23.34 ± 0.92[a, c]	62.50
10m[f]	12.53 ± 1.40[a]	79.87
Series B		
10g[f]	06.05 ± 1.14[a, c]	90.28
10h	33.48 ± 0.84[a,c]	46.21
10i[f]	05.08 ± 0.74[a,c]	91.84
10j	24.23 ± 1.33[a,c]	61.07
10k	17.03 ± 1.35[a,b]	72.64
10n	21.24 ± 1.46[a, c]	65.87
Series C		
13	47.00 ± 1.82[a, c]	24.49
14[f]	07.23 ± 0.82[a, b]	88.38
16	15.36 ± 1.38[a]	75.32

[a]$p < 0.01$ compared with control value. [b]$p < 0.05$ [c]$p < 0.01$ compared with indomethacin (5 mg/kg) value. [d]Each value represents the mean ± s.e.m. of the number of animals in each group (n = 6). [f]Represents the most active compound(s) in each series. [g]Compounds **10f** and **10i** untested.

is unsubstituted (R = H), the *p*-aminobenzoate ester **10m** induced the most significant inhibition (80%) in the weight of rat paw edema. This inhibitory effect was equipotent to the reference drug (81%). In "Series B", where the phenyl moiety is in position-2 of the ethanol linkage, both esters 4-bromophenylbenzoate **10i** and phenylbenzoate **10g** exhibited almost the same inhibitory activity (92% and 90%, respectively). This effect was nearly equipotent with that of indomethacin, which induced an 81% inhibition. This result shows that the anti-inflammatory profile is increased by the introduction of the aryl moiety **(Series B)** at the 2-position.

Concerning "Series C", 1-(4-amino-phenyl)-2-(1,7,7-trimethyl-bicyclo[2.2.1]hept-2-ylamino)-propane-1,3-diol (**14**) was the most active of the series, as it exhibited a significant inhibition in the weight of the rat paw edema (up to 88%) compared with the control and 39% with respect to indomethacin (5 mg/kg), whereas its N-methyl analogue **16** showed a 75% inhibition with respect to the control value at the same dose level.

Ulcerogenic effect. All the active anti-inflammatory compounds in the three series are found to be devoid of ulcerogenicity at the tested dose level (50 mg/kg) compared to the reference drug, indomethacin (5 mg/kg, ulcer index 21.6) [20].

CONCLUSIONS

Conclusively, the maximum anticonvulsant potency (100% protection) was displayed with compounds **16** (12.5 mg/kg), **10j** (50 mg/kg), **10h** (60 mg/kg), **10a** and **10e** (100 mg/kg), compared with diphenylhydantoin sodium (50 mg/kg, 100% protection) and deramciclane fumarate (25 mg/kg, 83% protection) as reference standards. Moreover, the same protective effect (83.3%) was achieved by compounds **14** (12.5 mg/kg), **10b** (50 mg/kg), **10c** (100 mg/kg) compared with deramciclane fumarate as reference standard, while diphenylhydantoin sodium, also used as reference standard, had a similar activity at 50 mg/kg. Moreover, the maximum hypoglycemic potency was displayed with esters **10b** (41%), **10d** (23%)**, 10e** (16.4%) and **10h** (14.4%), at a dose level of 50 mg/kg, compared with gliclazide, (23%, 10 mg/kg) as a reference drug. In addition, the maximum anti-inflammatory activity was displayed with compounds **10i** (92%), **10g** (90%), **14** (88%), **10m** (80%) at 50 mg/kg, while the reference drug showed an 81% anti-inflammatory activity, at a dose level of 5 mg/kg. Meanwhile, all the active anti-inflammatory compounds showed no sign of ulcerogenicity.

ACKNOWLEDGEMENTS

The authors appreciate the generous assistance of Prof. Dr. I.S. Ahmed Farag, X-ray Department, Physical Sciences Division, National Research Center, Cairo, for the performance of the high resolution of the single crystal X-ray crystallographic analyses and his valuable comments on the obtained data.

REFERENCES

[1] G. Buchbauer, S. Esterer, C. Cermak, Norbornane Compounds in Pharmaceutical Research. Die Pharmazie 38 (1983) 151.

[2] G. Buchbauer, H. Spreitzer, H. Frei, Norbornane Compounds in Pharmaceutical Research. Part 1. Pharmazie 46 (1991) 88.

[3] G. Buchbauer, I. Pauzenberger, Norbornane Compounds in Pharmaceutical Research. Pharmazie 54 (1999) 5.

[4] H. Kanerva, H. Vilkman, K. Nagren, O. Kilkku, M. Kuoppamaki, E. Syvalahti, J. Hietala, Psychopharmacology 145 (1999) 76.

[5] H. Kanerva, O. Kilkku, A. Helminen, J. Rouru, M. Scheinin, R. Huupponen, I. Klebovich, S. Drabant, A. Urtti, Int. J. Clin. Pharmacol. Therap. 37 (1999) 589.

[6] A.A. Al-Badr, S.E. Ibrahim, Pharmazie 37 (1982) 378.

[7] S. Schenone, O. Bruno, A. Ranise, F. Bondavalli, M. D'Amico, C. Vacca, M. Falciani, A. Filippelli, IL Farmaco 49 (1994) 545.

[8] S.S. Parmur, A.K. Gupta, T.K. Gupta, V.I. Stenberg, J. Pharm. Sci. 64 (1975) 154.

[9] C.A. Winter, E.A. Risley, G.W. Nuss, J. Pharmacol. Exp. Therap. 141 (1963) 369.

[10] M. Hernandez-Perez, R.M. Rabanal M.C. de la Torre, B. Rodriguez, M. Planta medica 61 (1995) 505.

[11] T. Corell, K.M. Jensen, J. Splawinski, Acta Pharmacol. Tox. 45 (1979) 232.

[12] H. Hoffmeister, B. Junge, Zeitschrift fur klinische Chemie und klinische Biochemie 8 (1970) 116.

[13] Marija J. Norusis/SPSS Inc., "SPSS for Windows", SPSS Inc. Marketing Department.Attn:Micro Software Products Manager, 444 N. Michigan Avenue, Chicago IL. 60611.

[14] F.S. Guziec, Jr, J.M. Russo, Synthesis (1984) 479.

[15] D.L. Gamble, W.P. Hems, B. Ridge, J. Am. Chem. Soc. Perkin Transactions 1 (2001) 248.

[16] D.H.R. Barton, W.B. Motherwell, E.S. Simon, S.Z. Zard, J. Am. Chem. Soc. Perkin Transactions 1 (1986) 2243.

[17] R. Bolton, T.N. Danks, J.M. Paul, Tetrahedron Lett. 35 (1994) 3411.

[18] M.D. Squire, A. Burwell, G.M. Ferrenece, S.R. Hitchcock, Tetrahedron Assymetr. 13 (2002) 1849.

[19] H.T. Clarke, H.B. Gillespie, S.Z. Weisshaus, J. Am. Chem. Soc. 55 (1933) 4571.

[20] Y.A. Maklad, A.A. E.Ahmed, New Egyptian J. Med. 26 (2002) 213.