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Synthesis of chloro and bromo substituted 5-(indan-1′-yl)tetrazoles and 5-(indan-1′-yl)methyltetrazoles as possible analgesic agents

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Received June 27, 2003, accepted October 3, 2003

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Pharmazie 59: 435–438 (2004)

Chloro and bromo substututed indanyl tetrazoles (compounds **5a, b**) and indanyl methyltetrazoles (compounds **5c**, **5d**) have been synthesized from their respective acids through amide and nitrile routes, and characterized. The title compounds (**5a**, **5b**, **5c** and **5d**) were subjected for their analgesic activity in the acetic acid induced writhing test on albino mice. The significant ($p < 0.001$) analgesic activity, exhibited by the compound **5b** at a dose of 50 mg/kg body weight, was comparable to that of phenylbutazone and indometacin at a dose of 100 and 50 mg/kg body weight respectively. The effect of substitution at the benzenoid part of the indan nucleus and chain lenght on analgesic activity was in the following order: bromine > chlorine and tetrazole > methyltetrazole.

1. Introduction

Tetrazole, an aromatic azapyrrole group, is metabolically stable (Figdor and Wittenau 1967), and has an acidic character closely similar to that of the carboxylic group (Herbst 1956). It has been reported that anti-inflammatory and related biological activities have been improved or abolished by the substitution of a 5-tetrazole group in place of a carboxyl function (Ganellin 1967). In this context a number of substituted 5-(indan-1′-yl)tetrazoles and 5-(indan-1′-yl)methyltetrazoles have been synthesized and investigated (Roy et al., 1983; Ray and Lahiri. 1990). Roy and Lahiri (1985) found that 5-(6′-methoxyindan-1′-yl)methyltetrazole and 5-(5′, 6′-dimethoxyindan-1′-yl)methyltetrazole were about four times less potent than phenylbutazone. In another experiment it was observed that none of the synthesized tetrazoles of simple, methoxy and dimethoxy substitution was comparable to the reference standard phenylbutazone or aspirin in a phenylquinone-induced writhing test (Ray et al. 1990). Since the chemical nature of halogens exerts a pronounced influence on the biological behavior of organic compounds, chlorine and bromine were incorporated at the 6-position in the benzenoid part of 5-(indan-1′-yl)tetrazoles and 5-(indan-1′-yl)methyltetrazoles to observe the improvement of biological activity in acetic acid induced writhing following the method of Vogel and Vogel (1997).

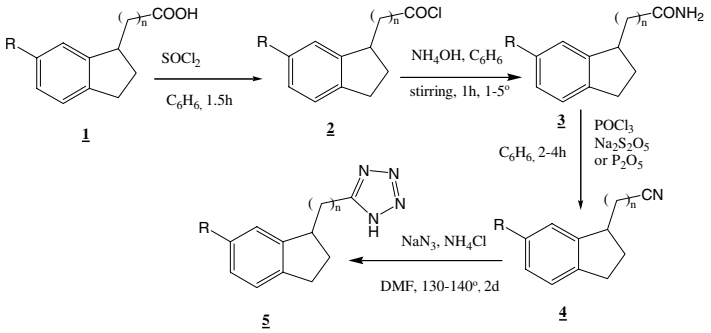
2. Investigations, results and discussion

The method of preparing the respective tetrazoles and methyltetrazoles is depicted in the Scheme. The compounds **5a, 5b, 5c** and **5d** were obtained by treatment of the respective acids **1** (Aono et al. 1977; Bachar and Lahiri 2000) with thionyl chloride in dry benzene refluxing for 1.5 h. The acid chlorides **2** thus obtained were immediately added to ammonia solution at 1–5 °C to give the respective substituted amides **3** in good yield. The amides **3** were then dehydrated with P_2O_5 in dry benzene or in a mixture of $POCl_3$ and NaS_2O_5 (10 : 1 ratio) refluxing for 2–4 h. After decomposing the reaction mixtures and working up, the respective nitriles **4** were obtained. Subsequently, the nitriles **4** were allowed to react with activated NaN_3 in presence of NH_4Cl in DMF at 130–140 °C for 2 d to give the target compounds 5-(6′-chloroindan-1′-yl)tetrazole (**5a**), 5-(6′-bromoindan-1′-yl)tetrazole (**5b**), 5-(6′-chloroindan-1′-yl)methyltetrazole (**5c**) and 5-(6′-bromoindan-1′-yl)methyltetrazole (**5d**) as crystalline powders.

The structures of the amides (**3a**, **3b**, **3c** and **3d**), nitriles (**4a**, **4b**, **4c** and **4d**), tetrazoles (**5a** and **5b**) and methyltetrazoles (**5c** and **5d**) were confirmed by various spectral and elemental analyses as mentioned in the experimental section. In ^{1}H NMR spectroscopy the two primary amide protons of the respective compounds were dropped by D_2O exchange spectrum. The IR spectrum of the nitriles showed characteristic absorption bands at 2236–2252 cm^{-1} ascribable to the CN functional group. Positive ion FAB MS or EI-MS of the respective Cl and Br substituted compounds exhibited pseudomolecular or molecular ion pairs with an increment of m/z value by two for their isotopes in the mass spectrum with relative abundance ratios 3 : 1 and 1 : 1 respectively.

The analgesic activity for acetic acid induced writhing was measured on albino mice for compounds **5a**, **5b**, **5c** and **5d**. The significant ($p < 0.001$) analgesic activity exhibited by compound **5b** at a dose of 50 mg/kg body weight was somewhat better than those of the reference standards phe-

Scheme



	a	b	c	d
R=	Cl	Br	Cl	Br
n=	0	0	1	1

Table: Analgesic activity of compounds 5-(6′-chloroindan-1′-yl)tetrazole (5a), 5-(6′-bromoindan-1′-yl)tetrazole (5b), 5-(6′-chloroindan-1′-yl)methyltetrazole (5c) and 5-(6′-bromoindan-1′-yl)methyltetrazole (5d) in the acetic acid induced writhing test

Treatment	Dose mg/kg body weight	Writhing	Writhing (Mean ± SE)	% Inhibition
Compound **5a**	25	26, 22, 18, 19, 27, 17	21.50 ± 1.57	29.51[b]
	50	23, 24, 18, 15, 13, 20	18.83 ± 1.62	39.90[a]
Compound **5b**	25	22, 26, 18, 15, 16, 20	19.50 ± 1.52	36.06[a]
	50	10, 24, 16, 12, 14, 18	15.67 ± 1.85	48.62[a]
Compound **5c**	25	32, 19, 26, 22, 20, 27	24.33 ± 1.83	20.23[c]
	50	20, 27, 15, 17, 25, 23	21.17 ± 1.73	30.59[b]
Compound **5d**	25	21, 17, 26, 23, 28, 20	22.50 ± 1.50	26.23[b]
	50	14, 16, 26, 20, 21, 18	19.17 ± 1.57	37.15[a]
Phenylbutazone	100	25, 23, 18, 12, 13, 12	17.16 ± 2.15	43.38[a]
Indometacin	50	24, 20, 13, 16, 18, 25	19.33 ± 1.72	36.62[b]
Control	Saline	32, 34, 36, 28, 31, 22	30.50 ± 1.85	–

Probability values (calculated as compared to control using Student's t-test): a < 0.001, b < 0.01, c > 0.05
All values are means of six mice.

nylbutazone and indometacin at doses of 100 and 50 mg/kg body weight respectively. Compounds **5a** ($p < 0.001$) and **5d** ($p < 0.001$) at 50 mg/kg weight, and **5b** ($p < 0.001$) at 25 mg/kg body weight showed very similar therapeutic activity to that of indometacin and 8–17% less than phenylbutazone. This investigation revealed that compounds **5a**, **5b**, and **5d** exhibited good peripheral analgesic activity, which may be due to inhibition of peripheral nerve endings, which was better than the compounds synthesized and investigated before (Roy et al. 1983; Roy and Lihiri. 1985; Ray and Lahiri. 1990; Ray et al. 1990). The effect of substitution at the benzenoid part of the indan nucleus and chain lengthening on analgesic activity was approximately in the following order: bromine > chlorine and tetrazole > methyltetrazole respectively (Table).

3. Experimental

Melting points were determined on an Adco (India) apparatus and were uncorrected. IR spectra were taken on a U-270–30 IR spectrophotometer. ^{1}H NMR spectra were measured on a Varian VXR-500 spectrometer and a JEOL FX (400 MHz) spectrophotometer in $CDCl_3$ or DMSO-d_6 or acetone -d_6. ^{13}C NMR spectra were recorded on a JEOL FX (100 MHz) spectrophotometer using acetone-d_6. Chemical shifts were reported in δ (ppm) units downfield from tetramethylsilane, and the abbreviations of signal patterns are as follows: s, singlet; d, doublet; t, triplet; m, multiplet; br, broad. FAB-MS was taken on a Hitachi M80B mass spectrophotometer and EI-MS were carried out with a VG Micromass ZAB mass spectrophotometer. Elemental analyses were performed on a Perkin-Elmer CHN analyzer. Column chromatography was performed on silica gel (Merck).

3.1. Preparation of 6-haloindan-1-amides (**3**)

The respective indan-1-acids (**1**) (1mol) were treated with thionyl-chloride (1.5 mol) in dry benzene and refluxed for 1.5 h. The acid chlorides (**2**) thus formed were freed from excess $SOCl_2$ under vacuum and immediately dissolved in dry benzene. Then the solutions of compound **2** were added dropwise to an excess of ammonium hydroxide solution (50 ml) with stirring at 1–5 °C for 1 h. The reaction mixtures were saturated with sodium chloride and then extracted with benzene. The benzene layer of the respective compound was then vigorously shaken with saturated sodium bicarbonate solution washed with distilled water, and dried over anhydrous sodium sulphate. The benzene layers were then distilled off under reduced pressure and the solid masses thus obtained were recrystallized from alcohol-water mixture to obtain the compounds **3**.

3.1.1. 6-Chloroindan-1-carboxamide (**3a**)

Yield 4.67g (85%) colorless crystalline needles, m.p. 181–183 °C; IR (KBr, cm^{-1}): 3360, 3169 and 1650; ^{1}H NMR (acetone-d_6): δ 7.35 (s, H, 7-H), 7.22 (d, H, 5-H, J=8.0), 7.17 (d, H, 4-H, J = 8.0), 6.99 (brs, H, N-H), 6.36 (brs, H, N- H′), 3.96 (t, H, 1-H, J = 7.6, 7.2), 3.02 (ddd, H, 3- H′, J = 15.6, 5.2, 3.2), 2.84 (ddd, H, 3-H, J = 15.6, 8.4, 5.6), 2.47 (dddd, H, 2-H′, J = 12.4, 8.4, 7.6, 5.2) and 2.38 (dddd, H, 2-H, J = 12.4, 7.2, 5.6, 3.2); ^{13}C NMR (acetone-d_6): δ 174.5 (C=O), 145.8 (C-6), 143.8 (C-7), 131.8 (C-5), 127.4 (C-4), 126.3 (C-8), 125.0 (C-9), 51.7 (C-1), 32.0 (C-3) and 29.2 (C-2); FAB$^-$MS (direct): m/z (%) 196.0534 [$M^+ + 1$] (34.0) and 198.0674 (11.1).
$C_{10}H_{10}ClNO$ (195.1)

3.1.2 6-Bromoindan-1-carboxamide (**3b**)

Yield 4.06 g (85%) colorless crystalline needles, m.p. 184–185 °C; IR (ν_{max}, KBr, cm^{-1}): 3330, 3160 and 1640; ^{1}H NMR (acetone-d_6): δ 7.50 (s, H, 7-H), 7.30 (d, H, 5-H, 7.2), 7.17 (d, H, 4-H, J = 7.2), 7.00 (brs, H, N-H), 6.37 (brs, H, N- H′), 3.98 (t, H, 1-H, J = 7.6, 7.2), 3.00 (ddd, H, 3-H′, J = 15.6, 5.2, 3.2), 2.80 (ddd, H, 3-H, J = 15.6, 8.4, 5.6), 2.35 (dddd,

H, 2-H′, J = 12.4, 8.4, 7.6, 5.2) and 2.25 (dddd, H, 2-H, J = 12.4, 7.2, 5.6, 3.2); ^{13}C NMR (acetone-d_6): δ 174.5 (C=O), 146.2 (C-6), 144.5 (C-7), 130.3 (C-5), 127.9 (C-4), 126.7 (C-8), 119.7 (C-9), 51.7 (C-1), 32.1 (C-3) and 29.0 (C-2); FAB$^-$MS (direct): m/z (%) 240.0018 [$M^+ + 1$] (19.4) and 242.01253 (19.0).
$C_{10}H_{10}BrNO$ (239.2)

3.1.3. 6-Chloroindan-1-acetamide (**3c**)

Yield 4.67 g (85%) as colorless crystalline needles; m.p. 115–116 °C; IR (ν_{max}, KBr, cm^{-1}): 3340, 3160 and 1600; ^{1}H NMR (acetone-d_6): δ 7.27 (s, H, 7-H), 7.19 (d, H, 5-H, J = 8.0), 7.13 (d, H, 4-H, J = 8.0), 6.85 (brs, H, N-H), 6.24 (brs, H, N-H′), 3.54 (ddd, H, 1-H, J = 7.6, 7.2, 6.4), 2.86 (ddd, H, 3-H′, J = 12.4, 8.0, 3.2), 2.76 (dd, H, 10-H′, J = 14.6, 7.6), 2.61(dd, H, 10-H, J = 14.6, 6.4), 2.34 (ddd, 3-H, J = 12.4, 4.4, 2.4), 2.30 (dddd, H, 2-H′, J = 13.2, 8.0, 7.2, 2.4), 1.74 (dddd, H, 2-H, J = 13.2, 8.0, 7.2, 2.4); ^{13}C NMR (acetone-d_6): δ 173.4 (C-11), 149.7 (C-6), 143.2 (C-7), 131.8 (C-5), 126.9 (C-4), 126.2 (C-8), 124.4 (C-9), 42.3 (C-1), 41.2 (C-10), 33.2 (C-3), 30.3 (C-2); FAB$^-$MS (direct): m/z (%) 210.0698 [$M^+ + 1$] (16.8) and 212.0872 (5.6).
$C_{11}H_{12}ClNO$ (209.1)

3.1.4. 6-Bromoindan-1-acetamide (**3d**)

Yield 5.01 g (90%) as colorless needles; m.p. 125–126 °C; IR (ν_{max}, KBr, cm^{-1}): 3360, 3180, 1600; ^{1}H NMR (acetone-d_6,): δ 7.42 (s, H, 7-H), 7.27 (d, H, 5-H, J = 7.2), 7.15 (d, H, 4-H, J = 7.2), 6.82 (brs, H, N-H′), 6.23 (brs, H, N-H), 3.56 (ddd, H, 1-H, J = 7.6, 7.2, 6.4), 2.85 (ddd, H, 3-H′, J = 12.4, 8.0, 3.2), 2.76 (dd, H, 10-H′, J = 14.8, 7.6), 2.61(dd, H, 10-H, J = 14.8, 6.4), 2.33 (ddd, H, 3-H, J = 12.4, 4.4, 2.4), 2.28 (dddd, H, 2-H′, J = 13.2, 8.0, 7.2, 2.4), 1.75 (dddd, H, 2-H, J = 13.2, 7.6, 4.4, 3.2); ^{13}C NMR (acetone-d_6): δ 173.3 (C-11), 150.1 (C-6), 143.7 (C-7), 129.8 (C-5), 127.4 (C-4), 126.7 (C-8), 124.4 (C-9), 42.3 (C-1), 41.3 (C-10), 33.3 (C-3), 31.2 (C-2); FAB$^-$MS (direct): m/z (%) 254.0190 [$M^+ + 1$] (25.9) and 256.0256 (25.1).
$C_{11}H_{12}BrNO$ (253.2)

3.2. Preparation of 6-haloindan-1-nitriles (**4**)

The 6-haloindan-1-amide compound **3** (1 mol) was mixed with P_2O_5 (5 mol) and refluxed for 2–4 h using dry benzene as the solvent (Roy et al. 1983). The reaction mixture was cooled and decomposed by addition of ice-water. Upon complete decomposition, it was extracted with benzene. The benzene layer was washed successively with 10% $NaHCO_3$ solution and distilled water; and dried over anh. Na_2SO_4. Alternatively the nitrile was prepared by dehydrating the amide. 6-haloindan-1-amide **3** (1 mol), $POCl_3$ (10 mol) and $Na_2S_2O_3$ (1 mol) were mixed in a RB flask. When the reaction began, the mixture was warmed to 70 °C on a water bath. The temperature was slowly raised to 95 °C where it was maintained for 2 h (Mihina and Herbst 1950). After quenching the reaction with ice, the nitriles **4a–d** were extracted with ether and dried over anh. Na_2SO_4. The dried ether layer or benzene layer was distilled off under reduced pressure. The residues obtained were crystalline solids for the carbonitriles (**4a** and **4b**) which were recrystallized from alcohol-water, and oils for the acetonitriles (**4c** and **4d**) which were vacuum distilled under reduced pressure.

3.2.1. 6-Chloroindan-1-carbinitrile (**4a**)

Yield 2.76 g (78%) as yellowish crystalline solid m.p. 73–74 °C; IR (ν_{max} KBr, cm^{-1}): 2236; ^{1}H NMR (DMSO-d_6): δ 7.46 (s, H, 7-H), 7.34 (s, 2 H, 5-H and 4-H), 4.47 (t, H, 1-H, J = 8.0, 7.5), 2.99 (ddd, H, 3-H′, J = 15.0, 5.5, 3.5), 2.88 (dddd, H, 2-H′, J = 12.5, 8.0, 6.0, 3.5), 2.54 (ddd, H, 3-H, J = 15.0, 7.0, 6.0), 2.26 (dddd, H, 2-H, J = 12.5, 7.5, 7.0, 5.5); FAB-MS (direct): m/z (%) 178.0231[M + 1] (26.2) and 180.0265 (8.4).
$C_{10}H_8ClN$ (177.1)

3.2.2. 6-Bromoindan-1-carboxnitrile (**4b**)

Yield 2.24 g (83%) as yellowish crystalline solid m.p. 65–66 °C; IR (ν_{max} KBr, cm^{-1}): 2236; ^{1}H NMR (DMSO-d_6): δ 7.58 (s, H, 7-H), 7.49 (s, 2 H, 5-H and 4-H), 4.54 (t, H, 1-H, J = 8.0, 7.5), 2.96 (ddd, H, 3-H′, J = 15.5, 7.0, 5.4), 2.82 (dddd, H, 2-H′, J = 12.0, 8.0, 7.0, 5.5), 2.41 (ddd, H, 3-H, J = 15.5, 5.5, 3.0), 2.12 (ddd, H, 2-H, J = 12.0, 7.5, 5.4, 3.0); FAB-MS (direct): m/z (%) 222.0764 [$M^+ + 1$] (17.3) and 224.0549 (16.8).
$C_{10}H_8BrN$ (221.2)

3.2.3. 6-Chloroindan-1-acetonitrile (**4c**)

Yield 2.71 g (79%) as light yellow oil b.p. 138–140 °C/0.6 mm-Hg, $\eta_{30} = 1.5543$); IR (ν_{max} KBr, cm^{-1}): 2252; ^{1}H NMR (DMSO-d_6) : δ 7.42 (s, H, 7-H), 7.27 (d, H, 4-H, J = 8.0), 7.24 (dd, H, 5-H, J = 8.0, 2.0), 3.45 (dddd, H, 1-H, J = 8.0, 7.5, 5.5, 3.5), 3.00 (ddd, H, 3-H′, J = 13.0, 6.5, 2.5), 2.96 (dd, H, 10-H, J = 13.5, 5.5), 2.92 (dd, H, 10-H′, J = 13.5, 3.5), 2.82 (dddd, H, 2-H′, J = 12.0, 8.0, 6.5, 3.0), 2.35 (ddd, H, 3-H, J = 13.0, 5.5, 3.0), 1.80 (dddd, H, 2-H, J = 12.0, 7.5, 5.5, 2.5); FAB-MS (direct): m/z (%) 192.0813 [$M^+ + 1$] (19.1) and 194.07980 (5.8).
$C_{11}H_{10}ClN$ (192.1)

3.2.4. 6-Bromoindan-1-acetonitrile (**4d**)

Yield 3.16 g (86%) as light yellow oil b.p. 120–122 °C/1.6 mm-Hg, $\eta_{30} = 1.5622$); IR (ν_{max} KBr, cm^{-1}): 2248; ^{1}H NMR (DMSO-d_6): δ 7.54 (s, H, 7-H), 7.41 (d, H, 4-H, J = 8.0), 7.28 (dd, H, 5-H, J = 8.0, 2.0), 3.55 (dddd, H, 1-H, J = 8.0, 7.5, 5.5, 3.5), 3.02 (ddd, H, 3-H′, J = 15.0, 6.5, 2.5), 2.86 (dd, H, 10-H, J = 13.5, 5.5), 2.80 (dd, H, 10-H′, J = 13.5, 3.5), 2.76 (dddd, H, 2-H′, J = 13.0, 8.0, 6.5, 3.5), 2.32 (ddd, H, 3-H, J = 15.0, 5.0, 3.5), 1.78 (dddd, H, 2-H, J = 13.0, 7.5, 5.0, 2.5); FAB-MS (direct): m/z (%) 235.0533 [$M^+ + 1$] (21.2) and 237.0764 (20.5).
$C_{11}H_{10}BrN$ (234.2)

3.3. Preparation of 5-(6′-haloindan-1′-yl)tetrazole (**5**)

The 6-haloindan-1-nitrile **4** (1 mol) with the addition of activated sodium azide (2 mol) and ammonium chloride (2 mol) was refluxed at 130–140 °C for 2 d using dimethylformamide (DMF) as the solvent following the method of Finnegan et al. (1958). Subsequently, the DMF was distilled off under reduced pressure and the solid mass obtained was taken up in warm 5% aqueous KOH solution. The cooled alkaline solution after filtration and subsequent ether extraction was made acidic (pH∼2) with conc. HCl. The precipitate thus obtained containing the desired compounds, 5-(6′-haloindan-1′-yl)tetrazoles **5a** and **5b**, and 5-(6′-haloindan-1′-yl)methyltetrazoles **5c** and **5d**, was washed with water and recrystallized from hot water.

3.3.1. 5-(6′-Chloroindan-1′-yl)tetrazole (**5a**)

Yield 1.31 g (50%) as a light yellow powder m.p. 185–186 °C; IR (ν_{max}, KBr, cm^{-1}): 1576, 1258, 1162; ^{1}H NMR (DMSO-d_6): δ 7.34 (d, H, 4-H, J = 8.0), 7.28 (dd, H, 5-H, J = 8.0, 2.0), 7.18 (brs, H, 7-H), 4.81 (t, H, 1-H, J = 8.0, 8.0), 3.05 (m, H, 3-H′, J = 16.0, 8.5, 4.5), 2.97 (ddd, H, 3-H, J = 16.0, 8.2, 7.8), 2.60 (dddd, H, 2-H′, J = 12.6, 8.5, 8.0, 7.8) and 2.33 (dddd, H, 2-H, J = 12.6, 8.2, 8.0, 4.5); EI-MS (70 eV): m/z (%) 220.3 [M^+] (87) and 222.2 (30), 185 (56), 151 (100), 116 (71), 89 (22), 75 (10) (corresponds to the fragments).
$C_{10}H_9ClN_4$ (221.1)

3.3.2. 5-(6′-Bromoindan-1′-yl)tetrazole (**5b**)

Yield 0.963 g (52%) as a light yellow powder m.p. 191–192 °C; IR (ν_{max}, KBr, cm^{-1}): 1586, 1265, 1160; ^{1}H NMR (DMSO-d_6) : δ 7.35 (d, H, 4-H, J = 7.9), 7.29 (dd, H, 5-H, J = 7.9, 2.0), 7.19 (brs, H, 7-H), 4.80 (t, H, 1-H, J = 8.3, 7.8), 3.06 (ddd, H, 3-H′, J = 16.0, 8.6, 4.5), 2.98 (ddd, H, 3-H, J = 16.0, 8.0, 7.0), 2.61 (dddd, H, 2-H′, J = 12.5, 8.6, 8.3, 7.0), 2.33 (dddd, H, 2-H, J = 12.5, 8.0, 7.8, 4.5); EI-MS (70 eV): m/z (%) 264.3 [M^+] (58) and 266.3 (57), 195 (100), 185 (51), 116 (68), 89 (20), 75 (12) (corresponds to the fragments).
$C_{10}H_9BrN_4$ (263.2)

3.3.3. 5-(6′-Chloroindan-1′-yl)methyltetrazole (**5c**)

Yield 1.24 g (53%) as a brown powder m.p. 143–144 °C; IR (ν_{max}, KBr, cm^{-1}): 1602, 1306, 1176; ^{1}H NMR (DMSO-d_6): δ 7.23 (s, H, 7-H), 7.21 (dd, H, 5-H, J = 8.0, 1.7), 7.19 (d, H, 4-H, J = 8.0), 3.71 (dddd, H, 1-H, J = 8.0, 6.8, 6.0, 5.0), 3.44 (dd, H, 10-H, J = 15.0, 5.0), 3.14 (dd, H, 10-H′, J = 15.0, 8.0), 2.81 (ddd, H, 3-H′, J = 14.5, 7.7, 2.2), 2.79 (ddd, H, 3-H, J = 14.5, 8.0, 2.0), 2.33 (dddd, H, 2-H′, J = 13.0, 8.0, 6.0, 2.2), 1.84 (dddd, H, 2-H, J = 13.0, 7.7, 6.8, 2.0); EI-MS (70 eV): m/z (%) 234.2 [M^+] (63) and 236.1 (20), 165 (100), 199 (50), 116 (75), 89 (20), 75 (12) (corresponds to the fragments).
$C_{11}H_{11}ClN_4$ (233.1)

3.3.4. 5-(6′-Bromoindan-1′-yl)methyltetrazole (**5d**)

Yield 1.39 g (50%) as a brown powder m.p. 149–150 °C; IR (ν_{max}, KBr, cm^{-1}): 1602, 1306, 1176; ^{1}H NMR (DMSO-d_6): δ 7.36 (s, H, 7-H), 7.34 (dd, H, 5-H, J = 8.0, 1.7), 7.25 (d, H, 4-H, J = 8.0), 3.60 (dddd, H, 1-H, J = 9.0, 8.0, 6.5, 5.5), 3.41 (dd, H, 10-H, J = 15.0, 5.5), 3.05 (dd, H, 10-H′, J = 15.0, 9.0), 2.83 (ddd, H, 3-H′, J = 16.0, 5.0, 3.0), 2.72 (ddd, H, 3-H, J = 16.0, 8.5, 7.5), 2.18 (dddd, H, 2-H′, J = 12.5, 7.5, 6.5, 5.0), 1.75 (dddd, H, 2-H, J = 13.0, 7.7, 6.8, 2.0); EI-MS (70 eV): m/z (%) 278.3 [M^+] (37) and 278.1 (36), 209 (100), 199 (56), 116 (72), 89 (24), 75 (14) (corresponds to the fragments).
$C_{11}H_{11}BrN_4$ (277.2)

3.4. Preparation of activated NaN_3

Sodium azide (10 g) was placed in a glass mortar, and 5–8 drops of hydrazine hydrate were added to it. The mixture was triturate and kept over night. The mixture was dissolved in 8–10 ml of water in a beaker and acetone (500–600 ml) added until a precipitate was formed. It was kept undisturbed for 2 hours. The crystals were then collected by filtration and dried.

3.5. Analgesic activity

Adult Swiss albino mice aged 4 to 5 weeks weighing 20 to 25 g were used to study the analgesic activity by acetic acid induced writhing as described by Vogel and Vogel (1997) with little modifications. Animals were divided into different groups consisting of six each. Compound **5a**, **5b**, **5c** and **5d** were given orally to the respective groups of animals at dose levels of 25 and 50 mg/kg body weight and the reference standards phenylbutazone and indometacine were given to two different groups at dose levels of 100 and 50 mg/kg body weight respectively. One group was kept as a control and given saline solution only. Forty minutes after drug administration acetic acid solution (0.7%, 0.10 ml/10gm) was administered intraperitoneally (i.p.) to each group of animals. After an interval of 10 min, writhing numbers were counted for another 10 min. The percent inhibition of analgesic activity was measured using the formula

$$\text{Percent inhibition} = \frac{W_c - W_t}{W_c} \times 100$$

Where W_c represents the average writhing produced by the control group and W_t represents the average writhing produced by the test group respectively.

Acknowledgement: The authors are grateful to the Ministry of Science and Technology, Government of Bangladesh, Dhaka, for granting a special allocation No. BPROMA/SHA-9/B: ANU:/2000/339 dt 22/05/2001 to perform some important parts of this project. The authors are indebted to Dr. A.S.S. Rouf, Associate Professor, Department of Pharmaceutics and Pharmaceutical Technology, University of Dhaka, for recording the NMR spectra when he was in Okayama University, Japan. They are also grateful to Dr. A. Rashid, Senior Research Scientist, National Cancer Institute, Frederick Cancer Research and Development Center, Maryland, USA and Professor, Department of Pharmaceutical Chemistry, University of Dhaka for recording mass spectra of some of the compounds.

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