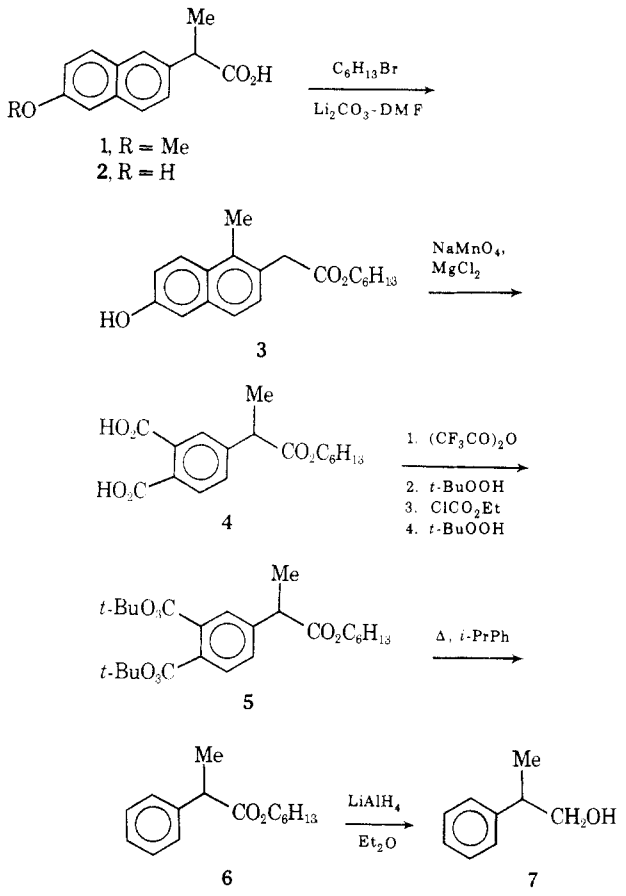
Scheme I



of tartaric acid has been determined[10] by a modified X-ray diffraction technique. It has thereby been shown[2] that (−)-2-phenylpropanol has the *S* configuration. Naproxen must also have the *S* configuration. The more active antipodes of antiinflammatory indan-1-carboxylic acids have previously been assigned the *S* configuration by ORD methods.[11] The ORD curve of naproxen was more complex than anticipated, precluding the use of this method.

Experimental Section

Melting points were taken on a Mel-Temp apparatus and are corrected. A Perkin-Elmer 137 spectrophotometer was used to record the ir spectra. Nmr spectra were determined on a Varian Associates HA-100 spectrometer using Me_4Si as internal standard. Optical rotations were measured with a Perkin-Elmer 141 polarimeter. Cyclohexanedimethanol succinate was used as stationary phase for gas chromatography. Satisfactory ir and nmr spectra were obtained for compounds **2**–**7**. Analyses indicated only by symbols of the elements were within ±0.4% of the theoretical values.

(+)-2-(6-Hydroxy-2-naphthyl)propionic Acid (2). A mixture of naproxen (**1**, 100 g, 0.43 mol), 48% HBr (250 ml), and AcOH (250 ml) was heated under reflux for 1.5 hr. Dilution of the cooled mixture with water followed by filtration gave **2** (81 g, 86%), mp 188–191°, $[\alpha]^{25}D$ +94° (Pyr), after recrystallization from EtOH. *Anal.* ($C_{13}H_{12}O_3$) C, H.

(+)-Hexyl 2-(6-Hydroxy-2-naphthyl)propionate (3). A mixture of **2** (14 g, 0.065 mol), Li_2CO_3 (14 g, 0.19 mol), hexyl bromide (20 g, 0.12 mol), and DMF (200 ml) was heated to 90° for 4 hr. After the addition of hexane and water, insoluble material was removed by filtration. The hexane layer was separated and washed with sodium bicarbonate solution and with water. Evaporation of solvent and excess hexyl bromide *in vacuo* gave **3** (18 g, 93%), mp 74–76°, $[\alpha]^{25}D$ +32° ($CHCl_3$), after recrystallization from hexane. *Anal.* ($C_{19}H_{24}O_3$) C, H.

(+)-Hexyl 2-(3,4-Dicarboxyphenyl)propionate (4). To a solution of the ester **3** (24 g, 0.08 mol) in acetone (400 ml) was added during 0.5 hr a solution of $NaMnO_4$ (20 g, 0.14 mol) and $MgCl_2$ (20 g, 0.21 mol) in water (75 ml) and the solution stirred for a further 3 hr. The precipitated MnO_2 was removed by filtration and washed with acetone and with water. The filtrate was acidified and extracted with ether. The acidic product was then extracted into sodium bicarbonate solution which was separated, acidified, and extracted with ether giving the acid **4** (2.1 g, 8%), $[\alpha]^{25}D$ +15° ($CHCl_3$).

Hexyl 2-(3,4-Di-*tert*-butylperoxycarbonylphenyl)propionate (5). A solution of **4** (410 mg, 1.27 mmol) in trifluoroacetic anhydride (5 ml) was kept at 20° for 30 min. Evaporation of the reagent and chromatography of the residue in CH_2Cl_2 on silica gel gave the anhydride (290 mg, 75%): ir (film) 1852, 1779 (anhydride) and 1730 cm^{-1}. *Anal.* ($C_{17}H_{20}O_5$) C, H. A solution of the anhydride (810 mg, 2.66 mmol) in dry benzene (6 ml) at 0° was treated with *tert*-butyl hydroperoxide (0.6 ml) and Et_3N (0.6 ml, 4.38 mmol). After 1 hr the solution was evaporated *in vacuo;* dry THF (8 ml) and Et_3N (0.37 ml, 2.7 mmol) were added and cooled to −25°. To this solution was added ethyl chloroformate (0.3 ml, 3.14 mmol) followed, after 30 min, by *tert*-butyl hydroperoxide (0.3 ml). After a further 30 min, the mixture was warmed up to −5° and a further quantity of Et_3N (0.37 ml, 2.7 mmol) was added. After an additional 1 hr, the mixture was poured into dilute HCl and ether. The ether layer was separated and washed with sodium bicarbonate solution and with water, and the solvent was removed giving **5** (420 mg, 71%).

Hexyl 2-Phenylpropionate (6) and 2-Phenylpropanol (7). A solution of the perester **5** (250 mg, 0.54 mmol) in isopropylbenzene (10 ml) was heated under reflux for 3 hr and the solvent fractionated off through a Vigreux column. The residue was distilled at 130° (bath temperature) and 3 mm of pressure giving **6** (64.5 mg, 51%). *Anal.* ($C_{15}H_{22}O_2$) H; C: calcd, 76.88; found, 77.38. A solution of **6** (64 mg, 0.27 mmol) in ether (10 ml) at 0° was treated with lithium aluminum hydride (150 mg, 3.9 mmol). After 1 hr excess reagent was decomposed by addition of acetone and water (1 ml). The mixture was filtered and the ether distilled from the filtrate giving **7** (35 mg, 94%), which was purified by gas chromatography. Pure material had the same retention time on 200-ft capillary columns as authentic samples: *m/e* 136 (M^+). The nmr spectrum (CCl_4) in the presence of tris[3-(trifluoromethylhydroxymethylene)-*d*-camphorato]europium was identical with that of authentic samples of (−)-**7**.

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Anticonvulsant Activity of Substituted Indolealkylamines†

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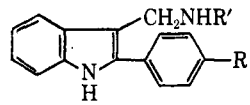
Administration of 5-hydroxytryptamine, an indolealkylamine, for several days has been shown to develop an an-

Table I. Substituted Indolealkylamines and Their Anticonvulsant Activity

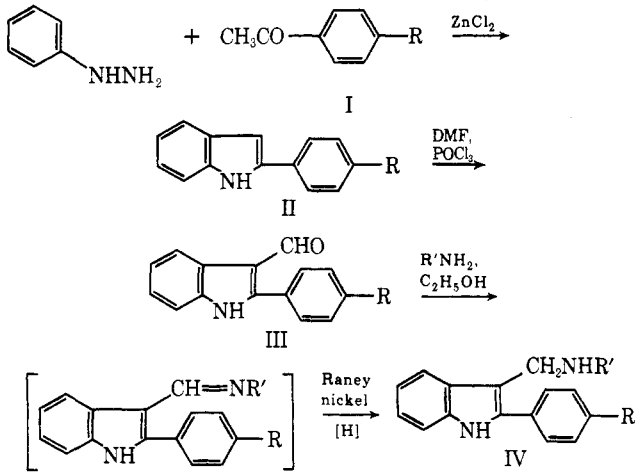


No.	R	R′	Mp, °C	Yield, %	Crystn solvent[a]	Mol formula[b]	Protection,[c] %	Mortality after 24 hr
1	H	$(CH_2)_3N(CH_3)_2$	144–145	50	EtOH	$C_{20}H_{25}N_3$	70	30
2	Cl	$(CH_2)_3N(CH_3)_2$	143–144	45	PhH–PE	$C_{20}H_{24}ClN_3$	50	40
3	CH_3	$(CH_2)_3N(CH_3)_2$	125–126	55	PhH–PE	$C_{21}H_{27}N_3$	70	30
4	H	Cyclopentyl	178–180	45	EtOH	$C_{20}H_{22}N_2$	30	70
5	Cl	Cyclopentyl	183	52	EtOH	$C_{20}H_{21}ClN_2$	40	50
6	CH_3	Cyclopentyl	165–167	55	EtOH	$C_{21}H_{24}N_2$	20	50
7	H	Cyclohexyl	168–170	60	EtOH	$C_{21}H_{24}N_2$	30	60
8	Cl	Cyclohexyl	225	55	EtOH	$C_{21}H_{23}ClN_2$	20	80
9	CH_3	Cyclohexyl	178–180	50	EtOH	$C_{22}H_{26}N_2$	60	30

[a] PE = petroleum ether. [b] All compounds were analyzed for C, H, and N and analyses were within ±0.4% of the theoretical value. [c] Approximate LD_{50} values of indolealkylamines were found to be greater than 1000 mg/kg.

tagonism toward pentylenetetrazole.[1] Indolealkylamines have also been shown to inhibit monoamine oxidase[2] which is responsible for biological inactivation of 5-hydroxytryptamine and other biogenic amines and is considered to play a role in the activity of the CNS. Inhibitors of monoamine oxidase have been shown to possess pronounced anticonvulsant properties.[3] In addition, CNS depressants have been shown to exert their effects by inhibiting certain metabolic processes in brain while selective inhibition of NAD-dependent oxidations was observed with 2-methyl-3-*o*-tolyl-4-quinazolone,[4] an anticonvulsant[5] and hypnotic[6] drug. These observations led us to synthesize substituted indolealkylamines as possible anticonvulsant agents. In the present study attempts have been made to correlate anticonvulsant activity possessed by the indolealkylamines with their ability to inhibit NAD-dependent oxidations by rat brain homogenates. The various substituted indolealkylamines were synthesized by following the steps outlined in Scheme I.

Scheme I



Experimental Section

The melting points were taken in open capillary tubes with a partial immersion thermometer and are uncorrected. All indolealkylamines were analyzed for C, H, and N and analyses were within ±0.4% of the theoretical value.

Substituted Acetophenones (I). Acetophenone,[7] *p*-chloroacetophenone,[8] and *p*-methylacetophenone[9] were prepared by following the methods reported earlier.

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Substituted Indoles (II). Addition of I to $PhNHNH_2 \cdot HCl$ was carried out in the presence of added anhydrous $ZnCl_2$ for the synthesis of 2-phenyl-,[10] 2-*p*-chlorophenyl-,[11] and *p*-methylphenylindoles.[12]

2-Substituted Indole-3-aldehydes (III). Formylation was carried out by refluxing a mixture of II, $POCl_3$, and DMF on a steam bath for 3–4 hr for the synthesis of 2-phenylindole-3-aldehyde,[13] 2-*p*-chlorophenylindole-3-aldehyde,[14] and 2-*p*-methylphenylindole-3-aldehyde.[15]

2-Substituted Indolealkylamines (IV). A mixture of an appropriate III (0.01 mol) and suitable alkylamine (0.01 mol) was dissolved in 150 ml of absolute EtOH. The mixture was hydrogenated in the presence of 0.1 g of Raney nickel at an initial pressure of 2.8 kg/cm². The required amount of H_2 was absorbed in 15 hr. The mixture was filtered and the excess of the solvent was removed from the filtrate under reduced pressure. The compounds which separated out on cooling were collected by filtration, washed, and recrystallized with suitable solvents. The substituted indolealkylamines were characterized by their sharp melting points and elemental analyses (Table I).

Biological Methods. Materials. AMP, cytochrome c, and α-ketoglutarate were obtained from Sigma Chemical Co., St. Louis; L-glutamic acid and sodium succinate were purchased from British Drug House, Bombay. Sodium β-hydroxybutyrate was obtained from Mann Research Laboratories, Inc., N. Y.

Enzyme Preparation. Male adult rats weighing approximately 200–250 g were sacrificed by decapitation. Brains were quickly removed and homogenized in ice-cold 0.25 *M* sucrose with the help of a Potter-Elvehjem homogenizer in the ratio of 1:9 (wt/v).

Assay Procedure. Earlier studies indicating equal inhibitory effectiveness of carbamides on the respiratory activity of mice or rat brain homogenates[16] led us to investigate the effects of substituted indolealkylamines on the respiratory activity of rat brain homogenates. Respiratory activity was determined by the conventional Warburg manometric technique at 37° using air as the gas phase. The reaction mixture in a total volume of 3 ml contained 6.7 m*M* $MgSO_4$, 20 m*M* Na_2HPO_4 in a buffer solution of pH 7.4, 1 m*M* AMP, 33 m*M* KCl, and 500 μg of cytochrome c. The central well contained 0.2 ml of 20% KOH. The indolealkylamines were dissolved in propylene glycol (100%) and an equal volume of propylene glycol was added to the control vessels.

Toxicity Studies. The approximate LD_{50} values of IV were determined in albino mice of either sex weighing 20–25 g.[17]

Anticonvulsant Activity. Mice of either sex weighing 20–25 g were divided in groups of ten, keeping the group weights near the same as possible. Various indolealkylamines were suspended in 5% aqueous gum acacia to give a concentration of 0.25% (wt/v). The test compounds were injected ip in a group of ten mice each at a dose of 100 mg/kg. Four hours after the administration of the test compounds the mice were injected sc with pentylenetetrazole (90 mg/kg). This dose of pentylenetetrazole has been shown to produce not only convulsions in almost all untreated mice but was also found to cause 100% mortality during the 24-hr period. On the other hand, no mortality was observed in mice treated with 100 mg/kg alone of the test compounds, and the animals were devoid of any behavioral effects. An episode of clonic spasm which persisted for a minimum period of 5 sec after the administration of pentylenetetrazole was considered a threshold convulsion. Transient intermittent jerks or tremulousness were not

Table II. Inhibitory Effects of Substituted Indolealkylamines on the Respiratory Activity of the Rat Brain Homogenate

Compd	Inhibition,[a] %				
	L-Glutamate	β-Hydroxybutyrate	α-Ketoglutarate	Pyruvate	Succinate
1	Nil	Nil	Nil	Nil	Nil
2	Nil	Nil	Nil	Nil	Nil
3	46.5 ± 1.2	85.7 ± 1.4	81.2 ± 1.0	82.5 ± 1.0	Nil
4	16.9 ± 1.5	42.1 ± 1.1	35.0 ± 1.1	11.2 ± 2.0	Nil
5	Nil	Nil	Nil	Nil	Nil
6	25.9 ± 0.8	24.1 ± 0.9	41.8 ± 2.1	12.3 ± 1.1	Nil
7	25.9 ± 0.7	59.4 ± 1.2	47.8 ± 1.3	63.5 ± 1.8	Nil
8	10.0 ± 0.8	29.5 ± 1.5	33.1 ± 1.7	23.1 ± 1.2	Nil
9	32.0 ± 1.0	64.8 ± 1.3	42.7 ± 1.0	25.6 ± 1.2	Nil

[a] Vessel contents and assay procedures are as described in the text. All values are the mean of three duplicate experiments. The per cent inhibition and the standard errors (S.E.) are calculated from the decrease in the oxygen uptake per hour per 100 mg of wet brain weight. The final concentrations of the various substrates and indolealkylamines used were 10 and 2 m*M*, respectively.

counted. Animals devoid of threshold convulsions during the period of 60 min were considered protected. The number of animals protected in each group was recorded and the anticonvulsant activity of the indolealkylamines was represented as per cent protection. The mice were then observed for a 24-hr period and their mortality was recorded.

Biological Results and Discussion

All indolealkylamines were found to exhibit anticonvulsant activity, maximum protection of 70% being observed with compounds **1** and **3** (Table I). Mortality observed during the 24-hr period has indicated that the compounds possessing greater anticonvulsant activity were found to cause the greatest decrease in mortality. Attachment of a CH_3 substituent at position 4 of the phenyl moiety attached at position 2 of the indole nucleus was found to have no effect on the anticonvulsant activity while the chloro substituent (compound **2**) showed decreased anticonvulsant activity. The nature of the substituent at the nitrogen atom of the alkylamino chain attached at position 3 of the indole nucleus was found to affect considerably the anticonvulsant activity of these indoles. Significant decrease in the anticonvulsant activity was observed by the substitution of cyclopentyl or cyclohexyl group for $(CH_2)_3N(CH_3)_2$. Such a decrease, however, was not much marked with compounds **2** and **9**. These results have thus indicated the sensitivity of substituents at the alkylamino side chain at the position 3 of the indole nucleus where anticonvulsant activity was found to be in the decreasing order of $(CH_2)_3N(CH_3)_2$ > cyclopentyl > cyclohexyl for these substituents. The approximate LD_{50} values, found to be greater than 1000 mg/kg, have revealed low toxicity of these indolealkylamines. All compounds, except compounds **1**, **2**, and **5**, were found to inhibit selectively the NAD-dependent oxidation of L-glutamate, β-hydroxybutyrate, α-ketoglutarate, and pyruvate at a final concentration of 2 m*M*. The NAD-independent oxidation of succinate, on the other hand, remained unaffected. Our results are similar to those observed with 2-methyl-3-*o*-tolyl-4-quinazolone where similar selective inhibition of the respiratory activity of rat brain homogenate has been reported.[4] In general, greater inhibition of the respiratory activity was observed during oxidation of β-hydroxybutyrate and α-ketoglutarate. It was interesting to note that compounds **1**, **2**, and **5** exhibiting 70, 50, and 40% protection, respectively, against pentylenetetrazole-induced seizures were found to possess no inhibitory effect on the respiratory activity of rat brain homogenate. Thus, in the present study no correlation could be observed with the anticonvulsant activity of these indolealkylamines and their ability to inhibit selectively the NAD-dependent oxidations. Determination of the effects of these compounds on other purified enzyme systems could possibly reflect the biochemical basis for the anticonvulsant activity of these substituted indolealkylamines (Table II).

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