Synthesis and pharmacological studies of 1-p-nitrobenzoyl-3-(3-substituted-2-hydroxypropyl oximinolo indole-2,3-diones

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Sodium salt of 3-oximinoi ndole-2,3-dione on reaction with epichlorohydrin in N,N'-dimethylformamide gives 3-(2,3-epoxypropyl oximino) indole-2,3-dione 2. Compound 2 on reaction with diverse secondary amines yields corresponding Mannich bases 3a-e, which on benzylation furnish 4a-e. The synthetic benzoyl derivatives of 4a-e have been screened for their pharmacological activities.

Indole derivatives are an important class of organic heterocycles because of their potential bioactivity as well as a part of several alkaloids. Indole derivatives are reported to be effective in CNS disorders such as convulsion and depression. Substituted arythiosemicarbazide derivatives of isatins were reported to be nontoxic and psychotropic. Several other indole derivatives are reported to be antimicrobial and anticonvulsant agents.

Aryloxopropanolamines are known to possess a number of biological activities, which include local anaesthetic, muscle relaxant and hypotensive, adrenolytic, tranquilizing, antiarrhythmic and diuretic activities.

Looking to the importance of these two types of compounds, we got interested to synthesise and screen the activity of propyloximino derivatives of indole.

Results and Discussion

3-oximinoindole-2,3-dione 1 was prepared conveniently employing the reported procedure. The sodium salt of 1 when reacted with epichlorohydrin in dry dimethyl formamide gave an oil of 3-(2,3-epoxypropyl oximino)indole-2,3-dione 2, which on further reaction with various secondary amines in methanol afforded 3-(3-substituted-2-hydroxypropyl oximino) indole-2,3-diones 3. These synthetic diones were subsequently transformed to the corresponding p-nitrobenzoyl derivatives 4 (Scheme I). The structures of all these compounds are established on the basis of spectral data.

\[ \text{Scheme I} \]

R = a. Piperdine, b. Pyroldine, c. Diethylamine,
d. Disopropylamine, e. Sodium azide

Note

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Pharmacological activity

All these synthetic compounds were screened for diverse pharmacological studies in mice following the method and score of system followed by literature procedure\(^1\).

Test compounds 4a and 4b demonstrated the significant antagonism of tetrabenzine induced ptosis whereas compounds 2 and 4e are found to be less active. This suggests that 4a and 4b possess antidepressant activity (Table I).

Further, the compounds 2, 4a, 4b and 4e were tested at a dose level of 50mg/kg and were found to reduce pentobarbitone sleeping time in mice by 9 to 32% over the untreated control. The results suggest that these compounds possess CNS activity (Table II).

Test compounds 4a and 4b have shown blockage of adrenaline induced contraction in rat vas deferens at a dose level of 2µg/mL (Table III).

Compounds 2 and 4e inhibited the adrenaline-induced relaxation at a dose level of 2 µg/mL. Compound 4e was found to be more active (77% inhibition) than compound 2 (52% inhibition), whereas 4a and 4b were found to be inactive. The inhibition of the adrenaline (2µg/mL) induced relaxation of rabbit jejunum by compounds 2 and 4e may be mediated through β-receptors because these compounds have not inhibited the adrenaline induced contraction of vas deferens of rat which is mediated through α-receptor (Table IV).

Test compounds 2 and 4e have completely blocked the histamine (2µg/mL) induced contraction in guinea pig ileum at dose level of 2 µg/mL whereas compounds 4a and 4b did not show any effect on the histamine induced contraction. Histamine acts on the H1 receptor in guinea pig ileum and produces contraction because this effect was completely blocked by compounds 2 and 4e (Table V).

Compound 2 has not shown any effect on blood pressure. Whereas compound 4b has shown first increase and then a persistent fall in blood pressure. After intravenous injection of compound 4a was given, blood pressure was further reduced and the animal died. Therefore, the compounds 4a and 4b may be used for controlling blood pressure.

Work is in progress to establish the utility of these compounds as active medicine.

Experimental Section

Melting points were taken in open capillary tubes and are uncorrected. Purity of the compounds was checked by TLC. IR spectra (νmax in cm\(^{-1}\)) were recorded on a Perkin-Elmer and \(^1\)H NMR spectra on a

<table>
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<th>Compd</th>
<th>Gr.</th>
<th>Avg body wt (g)</th>
<th>Dose (mg/Kg)</th>
<th>Avg ptosis at diff.interval (in min)</th>
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<td>I</td>
<td>19</td>
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<td>4 4 4 4 3.25 3.25 2 2</td>
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<tr>
<td>4a</td>
<td>II</td>
<td>19</td>
<td>50</td>
<td>4 4 3.25 3.25 2 2</td>
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<tr>
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<td>III</td>
<td>19</td>
<td>50</td>
<td>4 4 4 4 3.25</td>
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<tr>
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<td>IV</td>
<td>19</td>
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<th>Dose (mg/Kg)</th>
<th>Onset of action (min)</th>
<th>Avg. duration of deep sleep (min)</th>
<th>% decrease of sleeping time (min)</th>
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<th>Compd</th>
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<th>Adrenaline (2 µg/mL) height (in mm)</th>
<th>Adrenaline (2µg/mL) + Compd height (in mm)</th>
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<tr>
<td>4e</td>
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<td>37</td>
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### Table I — Antagonism of tetrabenzine ptosis in mice

### Table II — Potentiation of pentobarbitone narcosis in mice

### Table III — Inhibition of adrenaline effect on rat vas deferens in vitro
Perkin-Elmer 90 MHz spectrometer using TMS as internal reference.

3-Oximinoindole-2,3-dione 1. A solution of hydroxylamine hydrochloride (6.61g, 0.051mole) in water (5mL) was added to indole-2,3-dione (10g, 0.067mole) in 30mL of water contained in a 500mL wide necked flask equipped with a mechanical stirrer. This was followed by the addition of sodium acetate trihydrate (12.95g) in 30mL of water. The mixture was warmed with stirring at 60°C for 45 min. The mixture changed from deep red to light brown. The solution was kept overnight, filtered and washed with water. The yellow needles of 3-oximinoindole-2,3-dione 1 were recrystallised from ethanol (mp 224°C) (lit. mp 221°C) (Found: C, 67.62; H, 5.58; N, 14.28. Calcd for C12H12O3N4: C, 67.37; H, 5.64; N, 13.8%).

Preparation of 3-(3-substituted-2-hydroxypropyloximino)indole-2,3-dione 3. General procedure.
A solution of 2 (2g, 0.009mole) and a secondary amine (0.009mole) in methanol (100mL) was refluxed for 24hr. Excess solvent was removed under vacuo and the residue was taken up in chloroform (50mL). It was washed with 10mL of 1N HCl followed by 10mL of 1N NaOH and finally with water. The chloroform extract was dried and the solvent evaporated and the residue was chromatographed using petroleum ether-benzene (60-80°C) as eluent. Evaporation of the solvent gave 3a-e as wax like solid with very low melting point. 3a: mp 42°C, yield 75%; IR (KBr): 1700 (C=O), 1540 (C=N) cm-1; 1H NMR (CDCl3): 6.8-7.8 (m, ArH), 3.48 (d, -CH2), 3.9 (m, -CH), 2.6 (d, N-CH2), 2.74 (t, N-CH3), 2.5 (m, -CH2); Mass: m/z 304 (M-1), 86, 74, 51, 59 and 93.

Preparation of p-nitrobenzoyl derivatives 4a-e. Compounds 3a-e (0.0029mole) were dissolved in DMF (10mL) and p-nitrobenzoyl chloride (0.0029mole) was added to the above solution and the mixture refluxed for 2 hr. The reaction mixture was cooled to room temperature and poured into a beaker containing 100mL of water. The solid that separated out was filtered, washed with water and crystallised from acetonitrile. The structures of the benzoyl derivative 4a-e were established from spectral and elemental analyses.

4a: mp 224(86%), IR (KBr): 1696 (C=O), 3459 (-OH), 1542 (C=N), cm-1; 1H NMR (CDCl3): δ 8-7 (m, ArH), 3.48 (d, CH3), 3.9 (m, -CH), 2.6 (d, N-CH2), 2.74 (t, 1.5 (m) (Found: C, 68.27; H, 5.92; N, 13.8).
Caled for C15H13NO4: C, 68.32; H, 5.94; N, 13.86%.
4b: mp 220 (78%) (Found: C, 67.72; H, 5.58; N, 14.28). Caled for C15H13NO4: C, 67.69; H, 5.64; N, 14.35%.
4c: mp 230 (82%); 1H NMR (CDCl3): δ 8-7 (m,ArH), 3.48 (d, CH3), 3.9 (m, -CH), 1.6 (t, CH3) (Found: C, 67.37; H, 6.08; N, 14.2. Caled
for $C_2H_3O_2N_2$: C, 67.34; H, 6.12; N, 14.28%.

4d: mp 134 (90%); $^1$H NMR (CDCl$_3$): δ 7-8 (m, ArH), 3.48 (d, CH$_2$), 3.9 (m, CH), 2.6 (d, NCH$_2$), 4.2 (m, CH), 0.9 (d, CH$_3$) (Found: C, 68.51; H, 6.62; N, 13.28. Calcd for $C_2H_3O_2N_2$: C, 68.57; H, 6.66; N, 13.33%).

4e: mp 118 (64%) (Found: C, 59.61; H, 3.84; N, 23.19. Calcd for $C_2H_3O_2N_2$: C, 59.66; H, 3.86; N, 23.2%).

Acknowledgement
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References
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