

**4-Formylisochroman-1, 3 dione (II):** Homophthalic anhydride (I) (4.8 g) in dry methanol was added dropwise to a mixture of freshly prepared sodium methoxide (1.7 g) and ethyl formate (2.5 g) in methanol at 0–5° and left overnight. The reaction product was worked up in the usual way to give a white solid, recrystallized from hot water (2.15 g, 35%), m.p. 191–92°. It reduced Tollen's reagent. (Found C, 63.4; H, 3.06%, Calcd for C<sub>10</sub>H<sub>6</sub>O<sub>4</sub>; C, 63.15 H, 3.15).

**3-(4'-methoxyphenyl)-4-formylisocoumarin (III):** The dione II (2.06 g), anisole (1.1 g) and PPA (12.0 g) kept at 110–20° for 1.5 hr gave a product which on isolation and purification by the usual procedure gave a solid, crystallized from ethylacetate (1.3 g; 45%), m.p. 235–36°

$$\nu_{\text{max}}^{\text{KBr}} 1740, 1720, 1620, 1610 \text{ cm}^{-1};$$

$$\lambda_{\text{max}}^{\text{MeOH}} 312, 270, 261 \text{ nm}$$

(Found; C, 72.92; H, 4.13% Calcd for C<sub>17</sub>H<sub>12</sub>O<sub>4</sub>; C, 72.55, H, 4.28%)

**4-methoxy-w-(2'-carboxyphenyl)-formylacetophenone (IV):** Treatment of III (0.7 g) with aqueous sodium hydroxide 10% at room temperature, followed by acidification gave a solid recrystallized from EtOH, m.p. 110–111°.

$$\lambda_{\text{max}}^{\text{MeOH}} 275 \text{ nm}$$

(Found C, 68.49, H, 4.61%, Calcd for C<sub>17</sub>H<sub>14</sub>O<sub>5</sub>; C, 68.45; H, 4.69%)

**4-Methoxy-w-(2'-carboxyphenyl)-acetophenone (VI):** Isocoumarin III (0.70 g) was added with stirring to a suspension of freshly prepared silver oxide obtained from (0.5 g) silver nitrate in water (10 ml) and aqueous sodium hydroxide maintained at 55–60° for 20 min. Working up the reaction mixture in the usual way gave a solid, recrystallized as needles from EtOH, m.p. 170–71°, found identical with an authentic specimen

prepared earlier<sup>4</sup>.

$$\lambda_{\text{max}}^{\text{CHCl}_3} 270 \text{ nm}$$

(Found C, 71.08, H, 5.05%, Calcd for C<sub>16</sub>H<sub>14</sub>O<sub>4</sub>, C, 71.11, H, 5.18%)

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#### POSSIBLE ANTIPARKINSONIAN COMPOUNDS SYNTHESIS OF 2-STYRYL-3-ARYLTHIOURYL-3,4-DIHYDRO-4-OXOQUINAZOLINES

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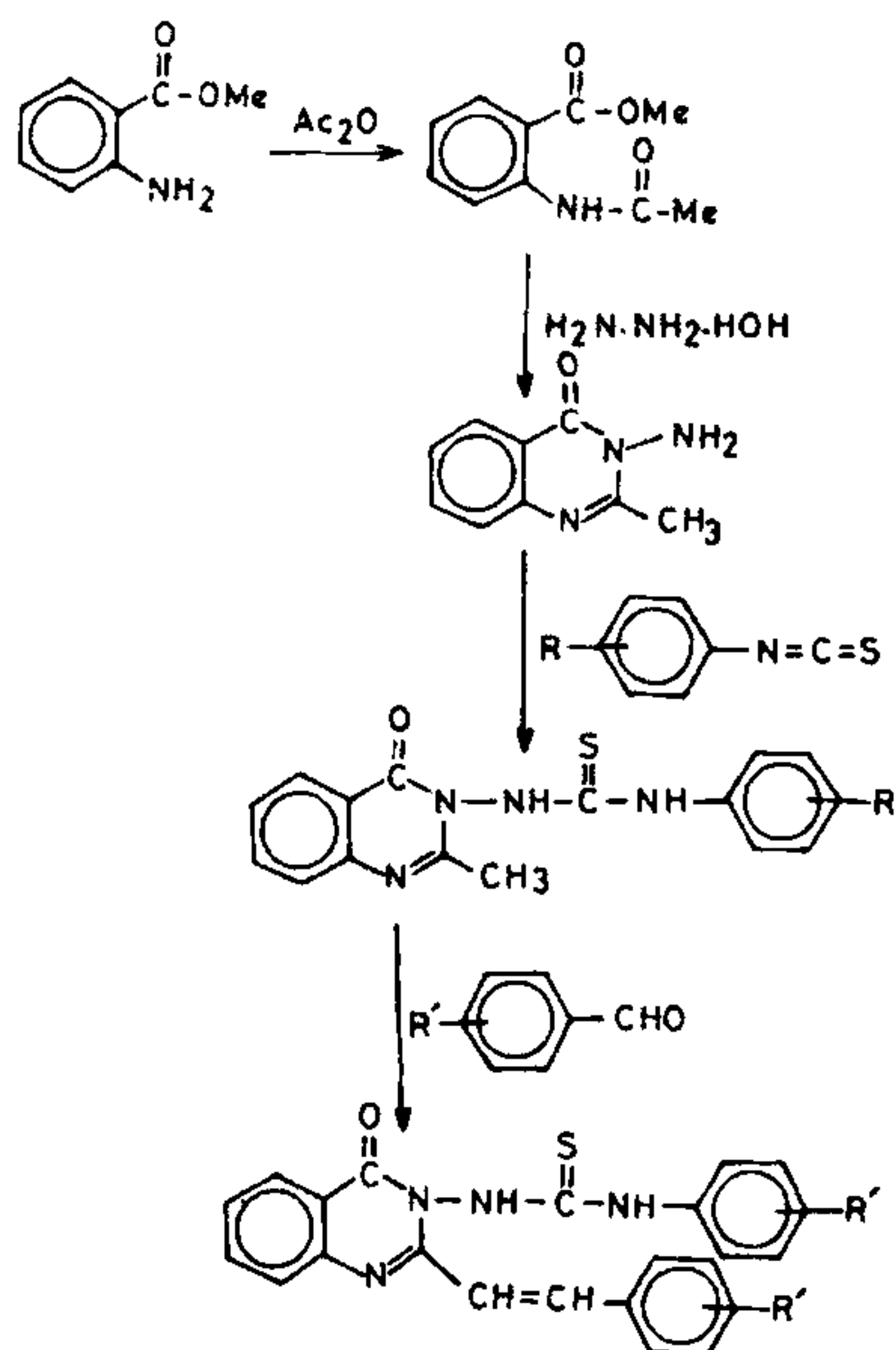
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TREATMENT of methyl anthranilate with acetic anhydride yielded methyl-N-acetylanthranilate which on treatment with hydrazine afforded 3-amino-3,4-dihydro-2-methyl-4-oxoquinazoline. 3-Amino-3,4-dihydro-2-methyl-4-oxoquinazoline was condensed with several arylisothiocyanates to give the corresponding arylthiourea derivatives. Interaction of 2-methyl-3-arylthiouryl-3,4-dihydro-4-oxoquinazoline with various aromatic aldehydes resulted in the corresponding styryl derivatives in the yields ranging from 40 to 50%.

The presence of quinazolone nucleus in a number of biologically active compounds and synthetic anti-pathogen led to a wider search in this group of compounds. Quinazolone derivatives have been reported to exhibit a wider range of biological activities like anticonvulsant<sup>1</sup>, antiparkinson<sup>2,3</sup>, antiviral<sup>4</sup>, antimalarial<sup>5</sup>, monoamineoxidase inhibitor<sup>6</sup> and central nervous system depressant<sup>7,8</sup>. The numerous CNS depressants and anticonvulsants have been shown to inhibit the respiratory activities of brain which ultimately lead to altered energy metabolism and neuronal functions<sup>9</sup>. On the basis of these valuable observations, some new

quinazolone derivatives have been synthesized to achieve better therapeutic results.

The synthesis was accomplished along the following route<sup>2</sup>. (Scheme 1)



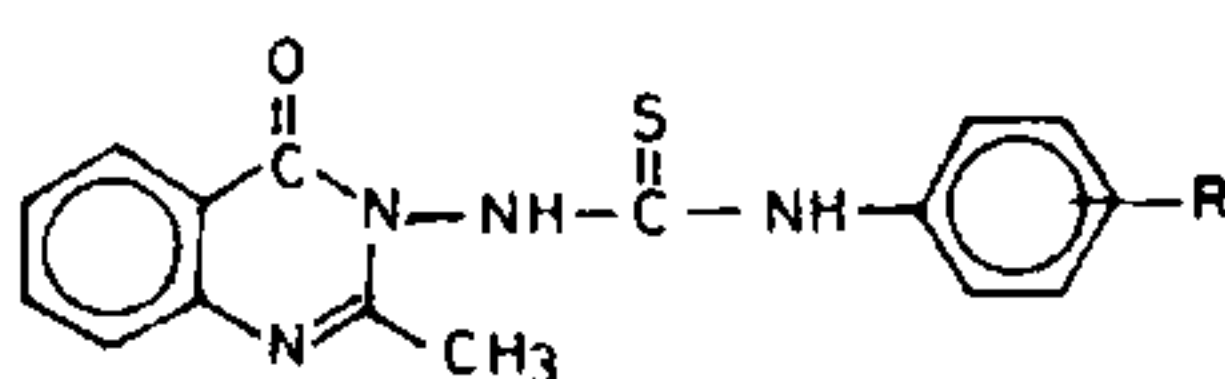
### Experimental

**Methyl-N-acetylanthranilate:** A solution of methyl-anthranilate (2.7 ml) in acetic anhydride (12 ml) was heated under reflux for 30 min. The solution was cooled and poured into cold water containing a drop of pyridine and stirred until the oil solidified. The crude product was filtered off, washed with water and dried at 100°. It was recrystallized from ethanol as colourless needles, m.p. 99–100° [100–101°]<sup>10</sup>.

**3-Amino-3,4-dihydro-2-methyl-4-oxoquinazoline:** A solution of hydrazine hydrate (10 ml) and methyl N-acetylanthranilate (2 g) in ethanol (25 ml) was heated under reflux for 2 hrs. The reaction mixture was cooled and stirred in cold water. A solid separated out, which was washed several times with water. The crude product was recrystallized from ethanol as colourless needles, m.p. 150°, [152–153°]<sup>11</sup>.

**2-Methyl-3-arylthiouryl-3,4-dihydro-4-oxoquinazoline:** A mixture of an equimolar amount of 3-amino-3,4-dihydro-2-methyl-4-oxoquinazoline and aryl-isothiocyanate in dry benzene was refluxed on a steam bath under anhydrous conditions for 5 hr. Subsequently the reaction mixture was cooled. A solid was separated which was repeatedly washed with water. It was recrystallized from dil. ethanol. The compounds thus synthesized are recorded in table 1.

**Table 1** 2-Methyl-3-arylthiouryl-3,4-dihydro-4-oxoquinazoline



Sl. No.	R	M.P. °C	Molecular formula	Analysis	
				Calcd.	Found
*1.	H	90	C <sub>16</sub> H <sub>14</sub> N <sub>4</sub> OS	18.06	18.21
2.	4-Me	125	C <sub>17</sub> H <sub>16</sub> N <sub>4</sub> OS	17.28	17.24
3.	3-Me	190	C <sub>17</sub> H <sub>16</sub> N <sub>4</sub> OS	17.28	17.32

(i) The above compounds were obtained in the yields varying from 50 to 60%.

(ii) Solvent for recrystallization was dilute ethanol.

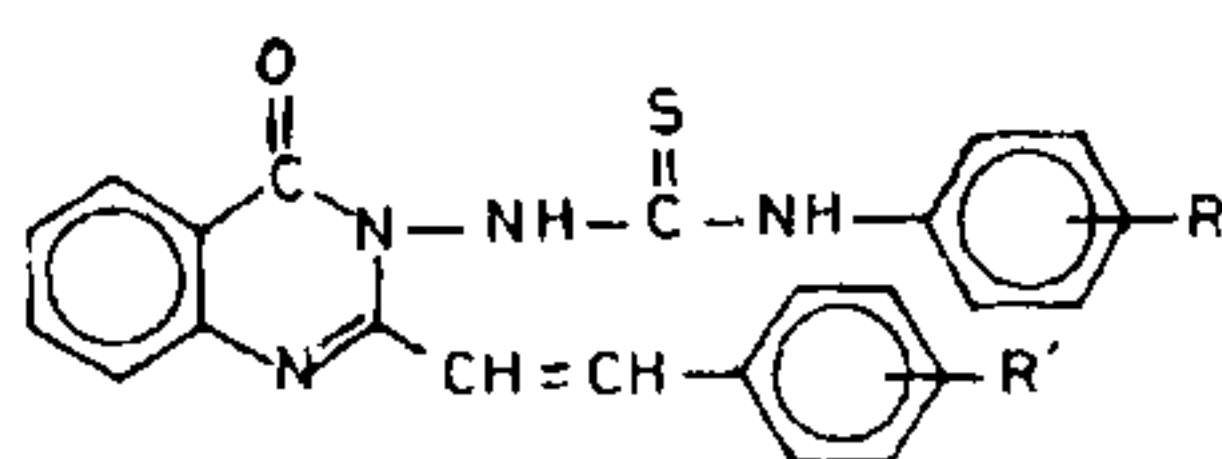
**IR(KBr)**  $\overset{\text{O}}{\parallel}$   
 1670 cm<sup>-1</sup> (—C— stretching in tertiary amide), 1660 cm<sup>-1</sup> (—C=N stretching), 3450 cm<sup>-1</sup> (—NH secondary), 1580 cm<sup>-1</sup> (N—H deformation).

**\*PMR(CDCl<sub>3</sub>)**

$\delta$ 2.2 (s, CH<sub>3</sub>),  $\delta$ 7.15 (s, phenyl) and  $\delta$ 8.2 (s, N—H— $\overset{\text{S}}{\parallel}$ C)



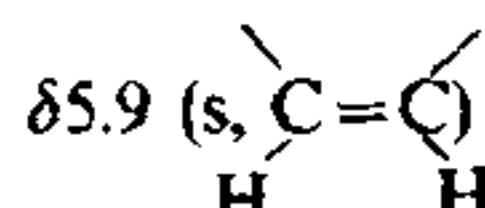
Table 2 2-Styryl-3-arylthiouryl-3,4-dihydro-4-oxoquinazoline



Sl. No.	R	R'	M.P. °C	Molecular formula	Analysis Nitrogen	
					Calcd.	Found
*1.	H	o-OCH <sub>3</sub>	180	C <sub>24</sub> H <sub>20</sub> N <sub>4</sub> O <sub>2</sub> S	13.08	13.21
*2.	H	o-OH	155	C <sub>23</sub> H <sub>18</sub> N <sub>4</sub> O <sub>2</sub> S	13.52	13.45
3.	4-CH <sub>3</sub>	o-CH <sub>3</sub>	170	C <sub>25</sub> H <sub>22</sub> N <sub>4</sub> O <sub>2</sub> S	12.66	12.50
*4.	4-CH <sub>3</sub>	o-OH	160	C <sub>24</sub> H <sub>20</sub> N <sub>4</sub> O <sub>2</sub> S	13.08	13.13
5.	3-CH <sub>3</sub>	2-OCH <sub>3</sub> 5-OH	110	C <sub>25</sub> H <sub>22</sub> N <sub>4</sub> O <sub>3</sub> S	12.22	12.25
6.	3-CH <sub>3</sub>	2-OH	95	C <sub>24</sub> H <sub>20</sub> N <sub>4</sub> O <sub>2</sub> S	13.08	13.38

Note: (i) The compounds were obtained in about 30 per cent yield (ii) The strong i.r. spectral bands at 1200 cm<sup>-1</sup> (for C=S stretching) and at 1670 cm<sup>-1</sup> (for C=O in amide) further supported the formation of these compounds.

\*PMR(CDCl<sub>3</sub>) δ7.5 (m, phenylprotons), δ5.5 (s, hydroxyl proton), δ3.5 (s, OCH<sub>3</sub>), δ8.2 (s, NH-C) and



+ UV λ<sub>max</sub> 278 nm (for HC=CH), λ<sub>max</sub> 203.5 and 254 nm. The last band consequent upon a forbidden π → π\* transition shows considerable fine structure and λ<sub>max</sub> 210 (absorption due to the phenolic moiety).

**2-Styryl-3-arylthiouryl-3,4-dihydro-4-oxoquinazoline:** A mixture of 2-methyl-3-arylthiouryl-3,4-dihydro-4-oxoquinazoline (0.001 mole) and aromatic aldehyde (0.0012 mol) in 30 ml of ethanol and 2 ml of 10% NaOH solution was heated under reflux for 4 hr. The solvent was distilled off under reduced pressure. The crude product, thus obtained, was washed repeatedly with water and recrystallized from ethanol. The compounds thus synthesized are listed in table 2.

#### Biological Activity

All the six compounds mentioned in table 2 were screened for their antioxotremorine activity in albino mice of either sex weighing 20–25 g each. After administering the test compounds intraperitoneally, for 1 hr, oxotremorine was injected to each mice. The maximum dose of oxotremorine to be injected was 5 mg/kg intraperitoneally. This dose of oxotremorine produced tremor and salivation in untreated animals. The animals were observed for the occurrence of tremor and salivation after 10 min.

#### Results

None of the compounds exhibited any significant antioxotremorine activity when administered intraperitoneally at 100 mg/kg dose. However, all the compounds were non-toxic (ALD<sub>50</sub> was > 1000 mg/kg, i.p.). Compound No. 1 exhibited considerable central nervous system depressant activity because this compound significantly increased the pentobarbitone sleeping time.

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## ROLE OF POLYPHOSPHOINOSITIDES IN BRAIN

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It is well known that the membranes of brain cells contain a high percentage of lipids which play a role in their structural and functional development. Among the brain lipids, polyphosphoinositides have the highest turnover and seem to play a leading role in signal transmission.

Studies carried out on the rat brain suggest that polyphosphoinositides exist as two different pools—one easily acted upon by hydrolases and the other not so easily hydrolyzed. For want of better nomenclature they are referred to as metabolically 'labile' and 'inert' pools<sup>1-3</sup>. The 'inert' pool may influence the structural integrity of the membrane whereas the 'labile' pool may be involved in cell proliferation and membrane function.

Recent studies show that the extracellular signals such as hormones, neurotransmitters, growth factors etc, combine with receptors in the brain cell membrane and activate enzymes which breakdown polyphosphoinositides. Originally, it was thought that phosphatidylinositol, 4,5-bisphosphate (PIP<sub>2</sub>) gets converted to phosphatidylinositol-4-phosphate (PIP), phosphatidylinositol (PI), 1,2-diacylglycerol and a mixture of inositol-1-phosphate (IP) and inositol 1,2-cyclic phosphate by sequential reactions. But recent studies have shown that extracellular signals activate phospholipase C which hydrolyses phosphatidyli-

nitol 4,5-bisphosphate (PIP<sub>2</sub>) to inositol trisphosphate (IP<sub>3</sub>) and diacyl glycerol (DG) which act as secondary messengers. Phosphatidyl inositol appears to be a precursor of PIP<sub>2</sub> and not a product of hydrolysis of PIP<sub>2</sub><sup>4</sup> (figure 1).

IP<sub>3</sub> stimulates the release of calcium from endoplasmic reticulum and prevents its reuptake<sup>5</sup>. At the same time, extrusion of calcium is prevented by the regulation of the calcium pump by membrane phosphoinositides. The possibility also exists that inositol 1,4-bisphosphate (IP<sub>2</sub>), a product of hydrolysis of phosphatidylinositol-4-phosphate (PIP), increases the permeability of plasma membrane to external calcium. The resulting increase in calcium facilitates events such as the release of neurotransmitters from the synaptic vesicles, activation of calcium/calmodulin-dependent protein kinase and activation of appropriate target enzymes<sup>6</sup>.

Two isomers of IP<sub>3</sub>, namely, 1,4,5-IP<sub>3</sub>, with a very short half-life, and 1,3,4-IP<sub>3</sub>, with a half-life of 30 min have been detected. The former is believed to be involved in releasing calcium from endoplasmic reticulum whereas the latter may help in transferring signals to the nucleus for cell division<sup>7</sup>. 1,3,4-IP<sub>3</sub> is not formed from 1,4,5-IP<sub>3</sub> and its mode of formation remains unknown.

In this connection it is tempting to suggest that two molecular species of PIP<sub>2</sub>—PIP<sub>2</sub><sup>1</sup> containing diacyl glycerol moiety with no arachidonic acid and 1,4,5-IP<sub>3</sub> moiety and PIP<sub>2</sub><sup>2</sup> containing diacylglycerol moiety with arachidonic acid and 1,3,4, IP<sub>3</sub> moiety—may be formed from PIP. The latter may be predominant during cell proliferation whereas the former may be predominant in the mature cell. Either the same phospholipase C or different isoenzymes may act on PIP<sub>2</sub><sup>1</sup> and PIP<sub>2</sub><sup>2</sup> (figure 2).

It is now suspected that the labile pool of polyphosphoinositides may turn out to be a mixture of different molecular species such as PIP<sub>2</sub><sup>1</sup>, PIP<sub>2</sub><sup>2</sup> etc.

1,4,5-IP<sub>3</sub> formed from PIP<sub>2</sub><sup>1</sup> may be the messenger needed for the release of calcium from endoplasmic reticulum. 1,3,4-IP<sub>3</sub> formed from PIP<sub>2</sub><sup>2</sup> may be involved in transferring signals to the nucleus for cell division during cell proliferation.

Diacylglycerol formed from PIP<sub>2</sub><sup>1</sup> may not contain arachidonic acid and may activate protein kinase C responsible for activating Na<sup>+</sup>/H<sup>+</sup> carrier involved in the influx of sodium into neurons during depolarization<sup>8</sup>. This may also activate calcium/phospholipid (phosphatidylserine) dependent protein kinase. But the physiological substrates for this kinase have not yet been identified.

Diacylglycerol formed from PIP<sub>2</sub><sup>2</sup> may contain