

## Synthesis of Some Substituted Quinazolones as Central Nervous System Depressants

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### Abstract

Some 2,3-disubstituted and 2,3,6-trisubstituted quinazolones have been synthesized from aminopyridines and tested for acetylcholinesterase and monoamine oxidase inhibitory properties. None of these compounds inhibited enzyme activity.

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Several 2,3-disubstituted quinazolones have been shown to possess central nervous system depressant activity. Some of these quinazolones were found to have hypnotic<sup>1)</sup> antiepileptic<sup>2)</sup>, antipyretic and hypothermic properties<sup>4)</sup>. 2-Methyl-3-ortho-tolyl-4-quinazolone was found to be a potent anticonvulsant superior to sodium phenobarbitone against metrazol induced seizures<sup>5)</sup>. Furthermore, it has recently been shown that 2-methyl-3-(4'-pyridyl)-4-quinazolone was devoid of antiacetylcholinesterase activity<sup>6)</sup> which was present in 4-aminopyridine<sup>7)</sup>. Quaternization of pyridinium nitrogen atom with various alkyl halides formed quaternary compounds which possessed enzyme inhibitory properties where maximum inhibition was observed with the quaternary compound synthesized from n-butyl iodide<sup>6)</sup>. On the basis of these observations several 2,3-disubstituted and 2,3,6-trisubstituted quinazolones from various substituted aminopyridines have been synthesized following the method of BOGERT et al.<sup>8)</sup>. In an

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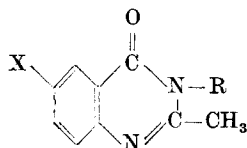
attempt to evaluate structure activity relationship of these quinazolones with respect to central nervous system depressant activity, we have investigated their effects on the activity of rat brain acetylcholinesterase and monoamine oxidase activity of the isolated rat liver mitochondria.

### Experimental<sup>9)</sup>

Acetantranil and 6-iodo-acetantranil were synthesized as reported earlier<sup>10)</sup>. Molar proportions of acetantranil and the appropriate aminopyridine were mixed together in a round bottom flask and heated first on a low flame and finally on a high flame. On cooling, the jelly like mass which separated out was crystallized with appropriate solvent yielding 2,3-disubstituted and 2,3,6-trisubstituted quinazolones in good yield.

The various aminopyridines used were, 2-amino-4-methylpyridine, 2-amino-6-methylpyridine, 2-amino-5-chloropyridine, 3-amino-2-chloropyridine and 5-amino-2-butoxypyridine hydrochloride. 5-Amino-2-butoxypyridine was isolated from its hydrochloride by treating with calculated amount of ammonia and extracting the base with ether. The characterization of these 2,3-disubstituted and 2,3,6-trisubstituted quinazolones was done by their sharp melting points and by analysis. The results are summarized in Table 1.

Table 1  
2-Methyl-3-R-4-Quinazolone



R	X	M.P. °C	Yield %	Formula	Solvent for crystallization	Analysis	
						% Calcd. N	% Found N
4-Methyl-2-Pyridyl HCl*)	H	234-237	60	C <sub>15</sub> H <sub>14</sub> ClN <sub>3</sub> O	EtOH - Ether	14.6	14.5
6-Methyl-2-Pyridyl HCl*)	H	198-201	55	C <sub>15</sub> H <sub>14</sub> ClN <sub>3</sub> O	EtOH - Ether	14.6	14.3
2-Chloro-3-Pyridyl	H	166	50	C <sub>14</sub> H <sub>10</sub> ClN <sub>3</sub> O	EtOH	15.5	15.18
5-Chloro-2-Pyridyl	H	142	40	C <sub>14</sub> H <sub>10</sub> ClN <sub>3</sub> O	EtOH + H <sub>2</sub> O	15.5	15.29
2-Butoxy-5-Pyridyl	H	239-241	80	C <sub>18</sub> H <sub>19</sub> N <sub>3</sub> O <sub>2</sub>	EtOH + Ether	13.5	13.2
4-Methyl-2-Pyridyl	I	193-196	50	C <sub>15</sub> H <sub>12</sub> IN <sub>3</sub> O	EtOH	11.14	10.9
6-Methyl-2-Pyridyl	I	173-175	52	C <sub>15</sub> H <sub>12</sub> IN <sub>3</sub> O	EtOH	11.14	10.92
2-Chloro-3-Pyridyl	I	198	45	C <sub>14</sub> H <sub>9</sub> IClN <sub>3</sub> O	EtOH	10.6	10.38
5-Chloro-2-Pyridyl	I	190-191	40	C <sub>14</sub> H <sub>9</sub> IClN <sub>3</sub> O	Acetone	10.6	10.9
2-Butoxy-5-Pyridyl	I	104-107	33	C <sub>18</sub> H <sub>18</sub> IN <sub>3</sub> O <sub>2</sub>	EtOH + Ether	9.7	9.4

\*) Compounds could not be recrystallized hence hydrochlorides were prepared.

<sup>9)</sup> Melting points are taken in capillary tubes and are graphically corrected.

<sup>10)</sup> K. KISHOR, R. C. ARORA and S. S. PARMAR, J. Med. Chem. 8, 550 (1965).

## Results

### Inhibition of acetylcholinesterase activity

Rat brains obtained from animals weighing approximately 150 g were homogenized in ice cold 0.25 M sucrose. The final concentration of the homogenate used throughout these studies without further purification was 10% (w/v). Acetylcholinesterase activity was determined colorimetrically using acetylthiocholine as the substrate where the enzymatically formed thiocholine contents were determined by the nitroprusside method<sup>11</sup>). All the quinazolone derivatives were found to have no effect on the activity of rat brain acetylcholinesterase at a final concentration of  $3 \times 10^{-3}$  M.

### Inhibition of monoamine oxidase activity

Monoamine oxidase activity was determined by the conventional WARBURG manometric method as described earlier<sup>12</sup>) using tyramine as the substrate. Rat liver mitochondria were isolated by differential centrifugation of rat liver homogenate in ice cold 0.25 M sucrose (10%; w/v) by the method of HOGEBOOM, SCHNEIDER and PALADE (1948)<sup>13</sup>). The mitochondrial preparation was washed 2 to 3 times with cold 0.25 M sucrose and finally suspended in the same concentration of sucrose so that 15 ml of the suspension was equivalent to 10 g of fresh liver. Oxygen uptake during oxidation of tyramine with such washed mitochondrial preparation has been shown to reflect the true monoamine oxidase activity<sup>14</sup>). None of these quinazolones were found to possess monoamine oxidase inhibitory property at a final concentration of  $3 \times 10^{-4}$  M.

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