

## Synthesis of Some Newer 3-Substituted-4(3H)-Quinazolones—Part I

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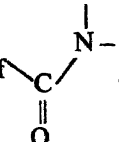
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Twenty-eight 3-alkyl and arylmethyl and seventeen 3-alkyl and arylaminomethyl substituted 4(3H)-quinazolones have been synthesized with a view to study their psychotropic properties.

QUINAZOLONES have been reported to exhibit pronounced CNS depressant<sup>1,2,3</sup>, anticonvulsant<sup>4,5</sup> and tranquilizing<sup>6</sup> effects with little or no side effects. Methaqualone, (2-methyl-3-*o*-tolyl-4 (3H) quinazolone) has remarkable hypnotic-sedative activity<sup>7,8</sup>.

It has been observed that the structure of most psychotropic agents consists essentially of one or two phenyl rings joined to a short alkyl chain of 2 to 3 carbon atoms bearing a substituted amino group, which may be part of a ring system<sup>9</sup>. It was, therefore, considered worth-while to synthesize some new 4 (3H)-quinazolones incorporating these structural features.

It has been observed<sup>10</sup> that methylation of 6-nitro-4(3H)-quinazolone afforded 6-nitro-3-methyl-4(3H)-quinazolone. In agreement with this we have also found that 4 (3H)-quinazolones easily undergo hydroxymethylation, chloromethylation and aminomethylation forming 3-hydroxymethyl, 3-chloromethyl and 3-aminomethyl-4 (3H)-quinazolones respectively, in good yield. These compounds were found to be high melting solids, slightly hygroscopic in nature. The 3-substituted-4 (3H)-quinazolones were then used to prepare various other compounds. Compounds thus synthesized, were characterized by their elemental, I.R. and N.M.R. analysis. The I.R. spectrum of 3-*o*-tolyliminomethyl-4 (3H)-quinazolone shows an intense band at 1642 cm<sup>-1</sup>

characteristic of  grouping and around 3185-

3450 cm<sup>-1</sup> for -NH group, in the N.M.R. spectrum a singlet due to methyl protons was observed at  $\delta$  2.40. Signal for N-CH<sub>2</sub>-N was observed at  $\delta$  4.12. A multiplet at  $\delta$  6.80-7.7 has been assigned to aromatic protons. The elemental analysis of all these compounds agree well with those calculated on the basis of the assigned structure.

The compounds were tested for CNS depressant activity in albino mice. All the compounds showed CNS depressant activity as is shown by loss of righting reflexes, ataxia and antimetrazol test. The approximate LD<sub>50</sub> of the compounds were found to possess in between 400 mg/kg to 800 mg/kg when the compounds were administered intraperitoneally in albino mice. The maximum percentage protection against pentylenetetrazol induced seizure in albino mice afforded by these substituted 4-quinazolones was found to be 80, where as some compounds did not show protection.

The detail of the CNS activity of these compounds will be published in due course.

### Experimental

Melting points were recorded in open capillaries in a sulphuric acid bath, and are uncorrected. Infrared spectra were determined in a Perkin-Elmer 137 spectrophotometer in KBr. N.M.R. spectra were recorded in a Perkin-Elmer R32 90 MHz spectrophotometer in DMSO-d<sub>6</sub> with TMS as internal standard. TLC was carried out using Kiessel gel G (according to Stahl) coated glass plates of 2 mm thickness.

#### 4-(3H)-Quinazolones(I) :

4-(3H)-quinazolones and halogen substituted 4(3H)-quinazolones were prepared according to the method described by Endicott *et al*<sup>11</sup>. 6-Nitro-4 (3H)-quinazolone was prepared according to the method described by Bogert *et al*<sup>12</sup>.

#### 3-Hydroxymethyl-4(3H)-quinazolone(II) :

To a suspension of 4(3H)-quinazolone (0.01 M) in 5 ml of distilled water was added 0.01M of 37% formaline. The reaction mixture was refluxed for 1-2 hr, on a steam bath and was allowed to remain at room temperature overnight. The white

crystalline solid thus obtained, was filtered, dried in air and recrystallized from ethanol.

### 3-Aminomethyl-4(3H)-quinazolones (I) :

To a suspension of 4(3H)-quinazolone (0.01 M) in 25 ml of ethanol was added 37% formaline (0.01 M) and ammonium chloride (0.01 M). The reaction mixture was refluxed for 2 to 3 hr on a steam bath and allowed to remain at room temperature overnight. The separated solid was filtered, dried in air and recrystallized from ethanol.

### 3-Chloromethyl-4(3H)-quinazolone hydrochloride (III) :

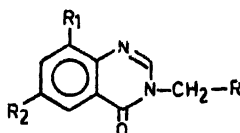
The appropriate 3-hydroxymethyl-4(3H)-quinazolone (0.01 M), anhydrous acetone (20 ml)

and HCl (1 ml) were refluxed on a steam bath for about 2 hr. The crystalline 3-chloromethyl-4(3H)-quinazolone monohydrochloride was occasionally deposited during the initial refluxing and was isolated by filtration and recrystallized from anhydrous acetone.

### 3-Phthalimidomethyl-4(3H)-quinazolone (VII) :

To a suspension of 3-hydroxymethyl-4(3H)-quinazolone (0.01 M) in ethanol (25 ml) was added with shaking phthalimide (0.01 M) in ethanol (25 ml). The reaction mixture was refluxed on steam bath for 4 hr and then allowed to remain at room temperature overnight. The solid product thus separated was filtered, dried and recrystallised from ethanol.

TABLE I



### 3-Alkyl/aryliminomethyl-4(3H)-quinazolones

Sl. No.	R <sub>1</sub>	R <sub>2</sub>	R	M.P.°C	Mol. formula	Analysis					
						Nitrogen%		Carbon%		Hydrogen%	
						Found	Calcd.	Found	Calcd.	Found	Calcd.
1.	H	H	OH	171	C <sub>8</sub> H <sub>8</sub> N <sub>2</sub> O <sub>2</sub>	15.92	15.90	61.22	61.96	4.48	4.55
2.	H	H	NH <sub>2</sub>	210-211	C <sub>8</sub> H <sub>8</sub> N <sub>2</sub> O <sub>2</sub> ·2HCl	17.21	17.01	48.36	48.72	3.02	3.23
3.	H	Br	NH <sub>2</sub>	180-82	C <sub>8</sub> H <sub>7</sub> N <sub>2</sub> OBr <sub>2</sub> ·2HCl	12.76	12.88	33.02	33.19	2.33	2.15
4.	Br	Br	NH <sub>2</sub>	above 280	C <sub>8</sub> H <sub>6</sub> N <sub>2</sub> OBr <sub>2</sub> ·2HCl	10.23	10.37	26.48	26.67	1.39	1.49
5.	H	Cl	NH <sub>2</sub>	193-195	C <sub>8</sub> H <sub>7</sub> N <sub>2</sub> OCl <sub>2</sub> ·2HCl	14.64	14.89	38.17	38.39	2.41	2.48
6.	Cl	Cl	NH <sub>2</sub>	225-226	C <sub>8</sub> H <sub>6</sub> OCl <sub>2</sub> ·2HCl	13.16	13.24	33.91	34.03	1.93	1.84
7.	H	NO <sub>2</sub>	NH <sub>2</sub>	226-228(d)	C <sub>8</sub> H <sub>7</sub> N <sub>2</sub> O <sub>2</sub> ·2HCl	19.08	19.17	36.82	36.99	2.6	2.4
8.	H	H	Cl	above 280	C <sub>8</sub> H <sub>7</sub> N <sub>2</sub> OCl <sub>2</sub> ·2HCl	10.27	10.49	40.27	40.45	2.41	2.25
9.	H	H	NHCOCH <sub>3</sub>	160-161	C <sub>11</sub> H <sub>10</sub> N <sub>2</sub> O <sub>2</sub> ·2HCl	14.34	14.52	45.43	45.67	3.51	3.46
10.	H	H	NHCH <sub>3</sub>	152-153	C <sub>10</sub> H <sub>10</sub> N <sub>2</sub> O <sub>2</sub> ·2HCl	16.11	16.09	45.36	45.98	3.79	3.82
11.	H	H	NH-CH(CH <sub>3</sub> ) <sub>2</sub>	170-172	C <sub>12</sub> H <sub>14</sub> N <sub>2</sub> O <sub>2</sub> ·2HCl	14.42	14.52	49.51	49.82	4.76	4.84
12.	H	H	N(CH <sub>3</sub> ) <sub>2</sub>	180-181	C <sub>11</sub> H <sub>12</sub> N <sub>2</sub> O <sub>2</sub> ·2HCl	15.12	15.27	47.91	48.00	4.22	4.36
13.	H	H	N(C <sub>2</sub> H <sub>5</sub> ) <sub>2</sub>	143-144	C <sub>13</sub> H <sub>16</sub> N <sub>2</sub> O <sub>2</sub> ·2HCl	13.21	13.89	51.22	51.48	5.41	5.61
14.	H	H	HN.CH <sub>2</sub> .CH <sub>2</sub> .OH	221-222	C <sub>11</sub> H <sub>12</sub> N <sub>2</sub> O <sub>2</sub> ·2HCl	14.11	14.42	45.26	45.36	4.01	4.11
15.	H	H	N(CH <sub>2</sub> .CH <sub>2</sub> .OH) <sub>2</sub>	227-228	C <sub>13</sub> H <sub>16</sub> N <sub>2</sub> O <sub>2</sub> ·2HCl	12.23	12.53	46.38	46.57	4.62	4.78
16.	H	H	phthalimido	194-195	C <sub>17</sub> H <sub>10</sub> N <sub>2</sub> O <sub>2</sub> ·2HCl	10.96	11.14	53.98	54.11	2.47	2.65
17.	H	H	HC(COOCH <sub>3</sub> ) <sub>2</sub>	204-205	C <sub>16</sub> H <sub>14</sub> N <sub>2</sub> O <sub>2</sub> ·2HCl	7.05	7.18	49.05	49.23	4.19	4.36
18.	H	H	HC(COOCH <sub>3</sub> ) <sub>2</sub>	197	C <sub>16</sub> H <sub>14</sub> N <sub>2</sub> O <sub>2</sub> ·2HCl	7.51	7.78	49.92	50.00	6.67	7.78
19.	H	H	N-Methylpiperazino	209-210	C <sub>14</sub> H <sub>17</sub> N <sub>2</sub> O <sub>2</sub> ·2HCl	16.72	16.97	50.12	50.31	5.08	5.15
20.	H	H	HN-CH <sub>2</sub> .COOH	210-211	C <sub>11</sub> H <sub>10</sub> N <sub>2</sub> O <sub>2</sub> ·3HCl	13.49	13.77	43.12	43.28	3.16	3.28
21.	H	H	NH.CH-CH <sub>2</sub> .COOH	200-201	C <sub>11</sub> H <sub>12</sub> N <sub>2</sub> O <sub>2</sub> ·2HCl	13.04	13.17	45.03	45.14	3.81	3.76
22.	H	H	NHCHCH <sub>2</sub> .CHCH <sub>2</sub>	248	C <sub>16</sub> H <sub>18</sub> N <sub>2</sub> O <sub>2</sub> ·2HCl	11.43	11.61	49.61	49.86	4.39	4.99
23.	H	H	NH-C <sub>6</sub> H <sub>5</sub>	168-69	C <sub>18</sub> H <sub>14</sub> N <sub>2</sub> O <sub>2</sub> ·2HCl	12.93	13.05	55.71	55.90	3.38	3.42
24.	H	H	NH-C <sub>6</sub> H <sub>4</sub> -p-Cl	232-23	C <sub>18</sub> H <sub>10</sub> N <sub>2</sub> O <sub>2</sub> Cl <sub>2</sub> ·HCl	11.94	11.76	50.24	50.42	2.58	2.80
25.	H	H	NH-C <sub>6</sub> H <sub>4</sub> -o-CH <sub>3</sub>	142-143	C <sub>18</sub> H <sub>14</sub> N <sub>2</sub> O <sub>2</sub> ·2HCl	12.21	12.46	56.71	56.97	4.21	4.15
26.	H	H	NH-C <sub>6</sub> H <sub>4</sub> -p-CH <sub>3</sub>	152-153	C <sub>18</sub> H <sub>14</sub> N <sub>2</sub> O <sub>2</sub> ·2HCl	12.27	12.46	56.68	56.97	4.19	4.15
27.	H	H	NH-C <sub>6</sub> H <sub>4</sub> -o-OCH <sub>3</sub>	246-247	C <sub>18</sub> H <sub>14</sub> N <sub>2</sub> O <sub>2</sub> ·2HCl	11.84	11.89	54.26	54.39	3.97	4.53
28.	H	H	NH-C <sub>6</sub> H <sub>4</sub> -p-OCH <sub>3</sub>	234-235	C <sub>18</sub> H <sub>14</sub> N <sub>2</sub> O <sub>2</sub> ·2HCl	11.81	11.89	54.21	54.39	3.81	4.53

All the compounds were obtained in 70-80% yield.

3-(2'-hydroxy-1'-phthalimidoethyl)-4 (3H)-quinazolinone (VIII):

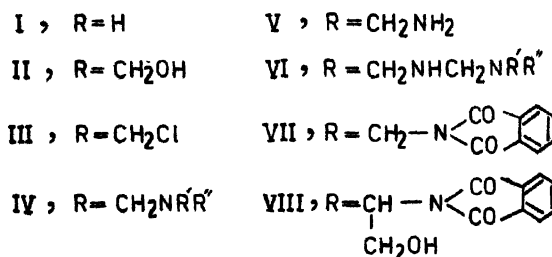
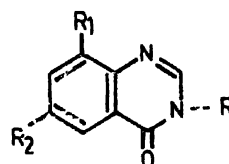
To a suspension of 3-phthalimidomethyl-4 (3*H*)-quinazolone (0.01 *M*) in ethanol (30 ml), was added with shaking 37% formaline (0.01 *M*) and sodium bicarbonate (0.2 g). The mixture was stirred for 8 hr at 35°. A clear solution first resulted and then crystals started separating. The reaction mixture was allowed to remain at room temperature overnight. The white crystalline solid thus obtained, was filtered, dried and recrystallized from ethanol, m.p. 185-187°, yield 80%.

**3-Alkyl and aryliminomethyl-4(3H)-quinazolones (IV) :**

To a suspension of 3-hydroxymethyl-4 (3*H*)-quinazolone (0.01 *M*) in absolute ethanol (15 ml), were added primary/secondary alkyl or aryl amine (0.01 *M*) and HCl dropwise so as to maintain the pH<7. The reaction mixture was then refluxed for 4 hr on a steam bath. The contents of the flask were allowed to cool. The solid 3-alkyl/aryliminomethyl-4 (3*H*)-quinazolone hydrochlorides thus separated, were recrystallized from ethanol and are recorded in the Table 1.

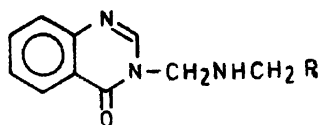
**3-Alkyl / aryl(bis-iminomethyl)-4(3H)-quinazolones (VI):**

3-Aminomethyl-4(3*H*)-quinazolinone (0.01 *M*) in ethanol (15 ml) on refluxing 3-4 hr on a steam bath with different reactive methylene compounds, phthalimide or with various alkyl or aryl bases (0.01 *M*) in the presence of 37% formaline (0.01 *M*) in acidic medium (Scheme I) yielded various new



### Scheme 1.

TABLE 2



3-Alkyl/aryl (bis-iminomethylene)  
-4 (3H)-quinazolones

Sl. No.	R	M.P.°C	Mol. formula	Analysis					
				Nitrogen %		Carbon %		Hydrogen %	
				Found	Calcd.	Found	Calcd.	Found	Calcd.
1.	HNCK,	205	C <sub>11</sub> H <sub>11</sub> N <sub>4</sub> O.2HCl	19.18	19.31	45.31	45.41	4.51	4.48
2.	NHCH(CH <sub>3</sub> ) <sub>2</sub> ,	198-199	C <sub>11</sub> H <sub>11</sub> N <sub>4</sub> O.2HCl	17.57	17.61	49.14	49.06	5.44	5.35
3.	N(CH <sub>3</sub> ) <sub>2</sub> ,	202-203	C <sub>11</sub> H <sub>11</sub> N <sub>4</sub> O.2HCl	18.48	18.42	47.49	47.37	4.98	4.93
4.	N(C <sub>2</sub> H <sub>5</sub> ) <sub>2</sub> ,	235-236	C <sub>11</sub> H <sub>11</sub> N <sub>4</sub> O.2HCl	16.69	16.87	50.42	50.60	5.67	5.72
5.	HNCH <sub>2</sub> CH <sub>2</sub> OH	190-191	C <sub>11</sub> H <sub>11</sub> N <sub>4</sub> O.2HCl	17.44	17.50	45.16	45.00	4.67	4.69
6.	N(CH <sub>2</sub> CH <sub>2</sub> OH) <sub>2</sub> ,	188-189	C <sub>11</sub> H <sub>11</sub> N <sub>4</sub> O.2HCl	15.29	15.38	46.32	46.15	5.37	5.22
7.	phthalimido	233-234	C <sub>11</sub> H <sub>11</sub> N <sub>4</sub> O.2HCl	13.46	13.79	53.12	53.20	3.31	3.20
8.	HC COOC(C <sub>2</sub> H <sub>5</sub> ) <sub>2</sub> ,	188-190	C <sub>11</sub> H <sub>11</sub> N <sub>4</sub> O.2HCl	10.12	10.02	48.58	48.69	4.58	4.78
9.	HC $\begin{matrix} \diagup \text{COCH}_3 \\ \diagdown \text{COOC(C}_2\text{H}_5\text{)}_2 \end{matrix}$	207	C <sub>11</sub> H <sub>11</sub> N <sub>4</sub> O.2HCl	10.69	10.79	49.26	49.36	5.61	5.40
10.	N-Methylpiperazino	192	C <sub>11</sub> H <sub>11</sub> N <sub>4</sub> O.2HCl	19.27	19.49	50.06	50.14	5.68	5.77
11.	HNCH <sub>2</sub> CH(OC <sub>2</sub> H <sub>5</sub> ) <sub>2</sub> ,	205-206	C <sub>11</sub> H <sub>11</sub> O <sub>2</sub> N <sub>4</sub> .2HCl	14.15	14.29	48.79	48.98	5.76	5.86
12.	NH-C <sub>6</sub> H <sub>4</sub> -o-CH <sub>3</sub> ,	292-293	C <sub>11</sub> H <sub>11</sub> N <sub>4</sub> O.2HCl	15.84	15.91	54.27	54.55	4.34	4.26
13.	NH-C <sub>6</sub> H <sub>4</sub> -p-Cl	195-196	C <sub>11</sub> H <sub>11</sub> N <sub>4</sub> OClHCl	14.28	14.47	49.47	49.61	3.41	3.62
14.	NH-C <sub>6</sub> H <sub>4</sub> -o-CH <sub>3</sub> ,	123-124	C <sub>11</sub> H <sub>11</sub> N <sub>4</sub> O.2HCl	15.36	15.30	55.61	55.74	4.47	4.64
15.	NH-C <sub>6</sub> H <sub>4</sub> -p-CH <sub>3</sub> ,	135-136	C <sub>11</sub> H <sub>11</sub> N <sub>4</sub> O.2HCl	15.32	15.30	55.31	55.74	4.51	4.64
16.	NH-C <sub>6</sub> H <sub>4</sub> -o-OCH <sub>3</sub> ,	213-214	C <sub>11</sub> H <sub>11</sub> N <sub>4</sub> O.2HCl	14.57	14.66	53.37	53.40	4.22	4.45
17.	NH-C <sub>6</sub> H <sub>4</sub> -p-OCH <sub>3</sub> ,	202-203	C <sub>11</sub> H <sub>11</sub> N <sub>4</sub> O.2HCl	14.49	14.66	53.26	53.40	4.51	4.45

- (1) All the compounds obtained as Hydrochloride.
- (2) These compounds were obtained in 60-80% yield.

3-alkyl (bis-iminomethyl) or aryl (bis-iminomethyl)-4 (3H)-quinazolones, which were recrystallized from ethanol and are recorded in the Table 2.

#### Acknowledgement

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