

# Synthesis and Spectral Study of 1-Methyl-2(R)-1,4-Dihydro-4-Oxoquinazoline Derivatives

N. R. NAIK, A. F. AMIN and S. R. PATEL

Department of Chemistry, Sardar Patel University, Vallabh Vidyanagar-388 120 (Gujarat)

Manuscript received 29 May 1978, revised 6 December 1978, accepted 27 April 1979

Arborine which is 1-methyl-2-benzyl-1, 4-dihydro-4-oxoquinazoline, and its 6- and 7-chloro, 6- and 7-nitro, 6-nitro-7-chloro, 6-chloro-8-nitro, benzo(6, 7) and 6,7-methylenedioxy derivatives and other 2-substituted derivatives have been prepared by treating corresponding N-methylantranilamide with the required acid chloride (RCOCl) in presence of a trace amount of pyridine in benzene. Their UV and IR spectral characteristics have been reported.

**A**RBORINE, an alkaloid isolated from a plant classified as *Glycosmis arborea* Correa is 1-methyl-2-benzyl-1,4-dihydro-4-oxoquinazoline<sup>1-3</sup>. In view of the interesting aspect of the structure and their possible physiological activity<sup>1</sup>, it was thought interesting to prepare benz-substituted derivatives of arborine including benzo(6, 7) derivative of arborine and other 1-methyl-2(R)-1, 4-dihydro-4-oxoquinazolines and studying their UV and IR spectral properties.

Three different methods for the synthesis of arborine have been reported in literature<sup>1,4,5</sup>. We have followed a method slightly different from the methods reported in literature. The synthesis of 1-methyl-2(R)-1, 4-dihydro-4-oxoquinazoline involves three steps in which the first two steps viz., synthesis of required N-methylisatoic anhydride and its aminolysis to N-methylantranilamide are the same as those in reported methods<sup>1,4</sup>. In the final step, N-methylantranilamide is transformed to the corresponding 1-methyl-2(R)-1, 4-dihydro-4-oxoquinazoline by treating it with the required acid chloride (RCOCl) in presence of a trace amount of pyridine in benzene.

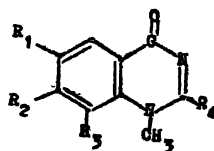
The N-methylisatoic anhydride is prepared by treating N-methylantranilic acid with ethylchloroformate in presence of acetyl chloride. The method is based on those reported in literature<sup>6,7</sup>. These isatoic anhydride derivatives are soluble in aqueous alkali and in ethylacetate, chloroform and ether.

The N-methylisatoic anhydride derivative on treatment with slight excess of liquor ammonia afforded corresponding N-methylantranilamide derivative in nearly quantitative yield<sup>4,7</sup>. The same product is formed when it is treated with varying amounts of ammonia. These N-methylantranilamide derivatives are described in Table 1. They are soluble in ethanol. They showed blue fluorescence in alcoholic solution. The N-methylantranilamide derivative on treatment with nearly equimolar amount of an acid chloride, RCOCl, in benzene in presence of a trace of pyridine afforded corresponding 1-methyl-2(R)-1, 4-dihydro-4-oxoquinazoline in the form of hydrochloride. The latter on treatment with aqueous ammonia afforded a free base. These compounds are described in Table 2.

TABLE 1—N-METHYLISATOIC ANHYDRIDE AND N-METHYLANTRANILAMIDE DERIVATIVES

R <sub>1</sub>	R <sub>2</sub>	R <sub>3</sub>	N-methylisatoic anhydride				N-methylantranilamide			
			m.p. °C	Mol. formula	% Nitrogen		m.p. °C	Mol. formula	% Nitrogen	
					Found	Calcd.			Found	Calcd.
H	H	H	180 <sup>7</sup> -61	C <sub>9</sub> H <sub>7</sub> O <sub>2</sub> N	7.8	7.9	162 <sup>7</sup>	C <sub>9</sub> H <sub>7</sub> O <sub>2</sub> N	18.5	18.7
Cl	H	H	198-200	C <sub>9</sub> H <sub>6</sub> O <sub>2</sub> NCl	6.5	6.6	183-85	C <sub>9</sub> H <sub>6</sub> O <sub>2</sub> NCl	15.1	15.2
H	Cl	H	218-20	C <sub>9</sub> H <sub>6</sub> O <sub>2</sub> NCl	6.4	6.6	197-98	C <sub>9</sub> H <sub>6</sub> O <sub>2</sub> NCl	15.0	15.2
NO <sub>2</sub>	H	H	217	C <sub>9</sub> H <sub>6</sub> O <sub>2</sub> N <sub>2</sub>	12.5	12.6	205	C <sub>9</sub> H <sub>6</sub> O <sub>2</sub> N <sub>2</sub>	21.3	21.5
H	NO <sub>2</sub>	H	243-46 (dec.)	C <sub>9</sub> H <sub>6</sub> O <sub>2</sub> N <sub>2</sub>	12.5	12.6	213-15	C <sub>9</sub> H <sub>6</sub> O <sub>2</sub> N <sub>2</sub>	21.4	21.5
NO <sub>2</sub>	Cl	H	218	C <sub>9</sub> H <sub>5</sub> O <sub>2</sub> N <sub>2</sub> Cl	10.8	10.9	262	C <sub>9</sub> H <sub>5</sub> O <sub>2</sub> N <sub>2</sub> Cl	18.1	18.3
Cl	H	NO <sub>2</sub>	183	C <sub>9</sub> H <sub>5</sub> O <sub>2</sub> N <sub>2</sub> Cl	10.8	10.9	199-200	C <sub>9</sub> H <sub>5</sub> O <sub>2</sub> N <sub>2</sub> Cl	18.2	18.3
6, 7-benzo		H	208-11	C <sub>11</sub> H <sub>7</sub> O <sub>2</sub> N	6.2	6.2	177-79	C <sub>11</sub> H <sub>7</sub> O <sub>2</sub> N	13.8	14.0
6, 7-O-CH <sub>2</sub> -O		H	205-07	C <sub>10</sub> H <sub>7</sub> O <sub>2</sub> N	6.5	6.3	173	C <sub>10</sub> H <sub>7</sub> O <sub>2</sub> N	14.3	14.4

TABLE 2—ARBORINE ANALOGUES AND THEIR SPECTRAL DATA



R <sub>1</sub>	R <sub>2</sub>	R <sub>3</sub>	R <sub>4</sub>	m.p. °C	Mol. formula	% Nitrogen		$\lambda_{\max}$ (log $\epsilon$ ) nm medium alcohol : water : 4 : 1	$\nu_{\text{C=O}}$ cm <sup>-1</sup>	$\nu_{\text{C=N}}$ cm <sup>-1</sup>
						Found	Calcd.			
H	H	H	CH <sub>3</sub>	209-11 <sup>7</sup>	C <sub>10</sub> H <sub>10</sub> ON <sub>2</sub>	15.9	16.1	229 (4.24), 265-305 (3.7-3.9)	1658	1621
H	H	H	C <sub>6</sub> H <sub>5</sub>	151-52	C <sub>11</sub> H <sub>11</sub> ON <sub>2</sub>	14.6	14.9	229 (4.26), 265-305 (3.7-3.9)	1658	1623
H	H	H	CH=CH-Ph	228-30 <sup>7</sup>	C <sub>17</sub> H <sub>14</sub> ON <sub>2</sub>	10.5	10.7	220 (4.42), 305 (4.13)	1657	1630
H	H	H	CH <sub>2</sub> -Ph	160-61 <sup>1,4</sup>	C <sub>16</sub> H <sub>14</sub> ON <sub>2</sub>	11.0	11.2	N : 231 (4.19), 266-306 (3.5-3.8) A : 235 (4.33), 270-305 (3.6-3.7) B : 233 (4.23), 268-305 (3.6-3.9)	1658	1626
H	H	H	Ph							
H	H	H	C=CH-Ph	234-36	C <sub>15</sub> H <sub>11</sub> ON <sub>2</sub>	8.1	8.3	230 (4.47), 275-305 (4.3-4.2)	1685	1621
H	H	H	Ph	178-79	C <sub>15</sub> H <sub>11</sub> ON <sub>2</sub>	11.7	11.9	231 (4.56), 280-305 (4.0-3.7)	1661	1631
Cl	H	H	CH <sub>3</sub>	150-51	C <sub>10</sub> H <sub>9</sub> ON <sub>2</sub> Cl	13.2	13.4	230 (4.63), 272-316 (4.2-3.8)	1667	1613
Cl	H	H	CH=CH-Ph	194-97	C <sub>17</sub> H <sub>11</sub> ON <sub>2</sub> Cl	9.2	9.4	222 (4.45), 295 (4.03)	1672	1613
Cl	H	H	CH <sub>2</sub> -Ph	174-75	C <sub>16</sub> H <sub>11</sub> ON <sub>2</sub> Cl	9.8	9.9	N : 231 (4.48), 279 (3.9), 316 (3.91) A : 231 (4.39), 277 (4.0), 304 (3.79) B : 225 (4.94), 277 (4.03), 315 (3.97)	1669	1618
Cl	H	H	Ph	203-05	C <sub>15</sub> H <sub>11</sub> ON <sub>2</sub> Cl	10.1	10.3	232 (4.67), 290-315 (4.3-1.0)	1667	1613
H	Cl	H	CH <sub>3</sub>	200-02	C <sub>10</sub> H <sub>9</sub> ON <sub>2</sub> Cl	13.1	13.4	233 (4.54), 274 (In)(4.15),		
H	Cl	H	CH=CH-Ph	290-98	C <sub>17</sub> H <sub>11</sub> ON <sub>2</sub> Cl	9.2	9.4	225 (4.48), 307 (3.87), 310 (4.16)	1675	1618
H	Cl	H	CH <sub>2</sub> -Ph	154-55	C <sub>16</sub> H <sub>11</sub> ON <sub>2</sub> Cl	9.7	9.9	N : 237 (4.49), 280-308 (3.6-4.0) A : 242 (4.55), 280-309 (3.6-3.8) B : 240 (4.50), 280-310 (3.6-3.9)	1661	1613
H	Cl	H	Ph	152-54	C <sub>15</sub> H <sub>11</sub> ON <sub>2</sub> Cl	10.2	10.3	240 (4.56), 280-298 (3.9-4.0)	1661	1605
NO <sub>2</sub>	H	H	CH <sub>2</sub> -Ph	288-90	C <sub>16</sub> H <sub>11</sub> O <sub>2</sub> N <sub>3</sub>	14.1	14.2	217 (4.28), 310-320 (4.1-4.2)	1692	1623
H	NO <sub>2</sub>	H	CH <sub>2</sub> -Ph	282-83	C <sub>16</sub> H <sub>11</sub> O <sub>2</sub> N <sub>3</sub>	14.4	14.2	235 (4.19), 260 (3.96), 280 (3.75)	1695	1627
NO <sub>2</sub>	Cl	H	CH <sub>2</sub> -Ph	312-14	C <sub>16</sub> H <sub>11</sub> O <sub>2</sub> N <sub>3</sub> Cl	12.5	12.7	228 (4.60), 289-308 (3.9-4.0)	1691	1628
Cl	H	NO <sub>2</sub>	CH <sub>2</sub> -Ph	292-94	C <sub>16</sub> H <sub>11</sub> O <sub>2</sub> N <sub>3</sub> Cl	12.6	12.7	239 (4.30), 265-336 (3.7-3.22)	1695	1626
6,7-benzo	H	H	CH <sub>2</sub> -Ph	218-20	C <sub>10</sub> H <sub>10</sub> ON <sub>2</sub>	9.1	9.3	N : 243 (4.59), 282 (4.30), 310 (4.47) A : 244 (4.42), 283 (4.43), 315 (3.52) B : 244 (4.72), 283 (4.49), 315 (4.4)	1648	1608
6,7-O-CH <sub>2</sub> -O	H	H	CH <sub>2</sub>	273-75	C <sub>11</sub> H <sub>10</sub> O <sub>2</sub> N <sub>2</sub>	12.7	12.8	243 (4.06), 319 (3.66), 332 (3.66)	1639	1605
6,7-O-CH <sub>2</sub> -O	H	H	CH <sub>2</sub> -Ph	231-33	C <sub>17</sub> H <sub>14</sub> O <sub>2</sub> N <sub>2</sub>	9.6	9.5	244 (4.44), 320 (4.0), 333 (4.01)	1639	1613
6,7-O-CH <sub>2</sub> -O	H	H	Ph	241-42	C <sub>16</sub> H <sub>14</sub> O <sub>2</sub> N <sub>2</sub>	10.2	10.0	248 (4.44), 324 (4.03), 333 (4.06)	1639	1600

N=neutral medium, A=acidic medium, B=basic medium.

They are highly soluble in ethanol, chloroform and acetone. UV spectra of these compounds were measured in 4 : 1 v/v ethanol-water mixture. The spectrum of each of these compounds comprises two bands. The low wavelength band of higher intensity (log  $\epsilon \sim 4.3$ ) appears around 230 nm and high wavelength band is a broad band extending from 265 nm to 305 nm with log  $\epsilon$  ranging around 3.8. The relevant data are presented in Table 2. Examination of these data reveals that the presence of any bz-substituent does not affect appreciably the nature of the band around 230 nm but it shifts the second long wavelength band to higher wavelength

or increases the intensity of the same band. In the spectrum of 1-methyl-2-benzyl-benzo(6,7)-1,4-dihydro-4-oxoquinazoline, both the bands have been shifted to higher wavelength and are of higher intensity. The UV spectra of 1-methyl-2-benzyl-1,4-dihydro-4-oxoquinazoline and its 6-chloro-7-chloro and benzo(6,7) derivatives have been studied in neutral, acidic and basic media. Comparison of the spectral characteristics of each of these compounds in three media reveals that the spectrum has not undergone any characteristic change with the change in the nature of the medium. This is in conformity with its structure. This rules out the

possibility of the compound existing in the enol form.

The IR spectra of 1-methyl-2(R)-1, 4-dihydro-4-oxoquinazoline derivatives were taken in KBr. The spectra showed presence of bands characteristic of  $-\text{CH}_2-$ ,  $>\text{C}=\text{O}$  of tertiary amide and of  $\text{C}=\text{N}$ . The positions of  $\text{C}=\text{O}$  and  $\text{C}=\text{N}$  bands are shown in Table 2. Examination of these data reveals that the position of  $\text{C}=\text{O}$  band is slightly shifted to higher frequency when Cl or  $\text{NO}_2$  groups are benz-substituents. In the spectrum of 6,7-methylenedioxy derivative of arborine the position of the  $\text{C}=\text{O}$  band is shifted to lower frequency. The position of  $\text{C}=\text{O}$  band is also lowered in the IR spectrum of benzo(6,7) derivative of arborine.

The 1-methyl-2-benzyl-1, 4-dihydro-4-oxoquinazoline derivatives gave on treatment with hot aqueous dilute alkali corresponding N-methylanthranilic acid. 1-Methyl-2-benzyl-1, 4-dihydro-4-oxoquinazoline, i.e., arborine yielded on reaction with benzaldehyde, 1-methyl 2-( $\alpha$ -phenylstyryl)-1, 4-dihydro-4-oxoquinazoline.

## Experimental

### *General method for preparing substituted-N-methylantranilic acid :*

A mixture of a solution of substituted anthranilic acid (1 g) in aqueous sodium hydroxide (12 ml, 0.7 M) and dimethylsulphate (0.6 ml) was stirred at room-temperature for an hour. The solid which separated out from the solution was collected, washed and crystallised from ethanol. Yield about 60 to 70%.

### *Preparation of benz-substituted-N-methylisatoic anhydride :*

Substituted-N-methylantranilic acid derivative (1 g) was refluxed with ethylchloroformate (5 ml) until the solution became clear. This required about three hours. Excess acetyl chloride (3 ml) was added to the cooled reaction-mixture and refluxed for two more hours till evolution of hydrogen chloride ceased. Acetylchloride was removed by distillation and the solid which separated out on cooling the reaction-mixture was filtered, washed with petroleum-ether and dried. It was crystallised from ethylacetate or benzene. Yield about 40-60%. The compounds are listed in Table 1.

### *Preparation of benz-substituted-N-methylantranilamide :*

A suspension of substituted-N-methylisatoic anhydride (1 g) in liquor ammonia (15 ml, 12 M) was stirred and heated on a boiling water-bath for nearly two hours. The cooled reaction-mixture was

filtered. The solid was crystallised from ethanol. Yield about 80-90%. The compounds are listed in Table 1.

### *Preparation of benz-substituted-1-methyl-2-benzyl (or R)-4-oxoquinazoline derivatives :*

A mixture of a solution of substituted-N-methylantranilamide (1 g) in dry benzene (10 ml) containing a drop of pyridine and phenylacetyl chloride (or  $\text{RCOCl}$ ) (1.6 ml) was refluxed at  $100-10^\circ$  for three hours with occasional stirring. Insoluble solid which separated out on cooling the reaction-mixture was filtered and washed with dry petroleum-ether. The compound was a hydrochloride. It afforded a free base on treatment with ammonia solution (5 ml, 8M) at room temperature. It was crystallised from ethanol or a mixture of ethanol-benzene (1 : 1). Yield about 50 to 65%. The compounds are listed in Table 2.

### *Reaction of 1-methyl-2-benzyl-1, 4-dihydro-4-oxoquinazoline with benzaldehyde : Formation of 1-methyl-2-( $\alpha$ -phenyl styryl)-1,4-dihydro-4-oxoquinazoline :*

A mixture of 1-methyl-2-benzyl-4-oxoquinazoline (0.2 g) and benzaldehyde (1 ml) was refluxed at  $170-80^\circ$  for two hours. The reaction-mixture was steam distilled to remove excess of benzaldehyde. The solid which separated on cooling the reaction-mixture was powdered, treated with bicarbonate solution and crystallised from ethanol in pale yellow plates. Yield 65%. The compound is listed in Table 2.

### *Reaction of 1-methyl-2-benzyl-1,4-dihydro-4-oxoquinazoline derivative with alkali solution :*

A suspension of 1-methyl-2-benzyl-1,4-dihydro-4-oxoquinazoline derivative (0.5 g) in aqueous sodium hydroxide (10 ml, 1M) was warmed on a water bath for an hour. During the progress of reaction, evolution of ammonia gas was detected. The cooled reaction-mixture was made just acidic. The solid which separated out was collected and washed. It was found to be corresponding N-methylantranilic acid. The filtrate was evaporated to one-third of its bulk. It was cooled and the solid which separated was collected and extracted with boiling ethanol. On evaporation of ethanol, solid remained. The latter was shown to be phenylacetic acid by comparing it with an authentic sample.

## References

1. D. CHAKRAVARTI, R. N. CHAKRAVARTI and S. G. CHAKRAVARTI, *J. Chem. Soc.*, 1953, 3337.

2. D. CHAKRAVARTI and R. N. CHAKRAVARTI, *Tetrahedron*, 1961, **16**, 224.
3. S. C. PAKRASHI and J. BHATTACHARYA, *Tetrahedron*, 1963, **19**, 1011.
4. A. CHATTERJEE and S. G. MAJUMDAR, *J. Amer. Chem. Soc.*, 1953, **75**, 4365 ; 1954, **76**, 2459.
5. S. C. PAKRASHI, A. DE and S. CHATTOPADHYAYA, *Indian J. Chem.*, 1968, **6**, 472.
6. BRÉDT and HOF, *Ber.*, 1900, **33**, 27.
7. I. M. HAILBORN, F. N. KITCHEN, E. B. PARKES and G. D. SUTTON, *J. Chem. Soc.*, 1925, 2167.
8. W. C. CUTTING, J. ROBERTS and P. TABER, *Med. Pharmacol. Exptl.*, 1966, **15**, 7.
9. R. E. LUTZ, J. F. CODINGTON and P. S. BAILEY, *J. Amer. Chem. Soc.*, 1946, **68**, 1810.
10. S. BOGERT, *J. Amer. Chem. Soc.*, 1919, **41**, 2066.
11. A. MEISELS and F. SONDHEIMER, *J. Amer. Chem. Soc.*, 1957, **79**, 6328.