

SEARCH FOR PHYSIOLOGICALLY ACTIVE COMPOUNDS

Part XV. Synthesis of Some (7, 8) Oxazolo-flavones

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ABSTRACT

The synthesis of a few (7, 8) oxazolo-flavones has been carried out starting from 7-hydroxy-8-amino flavone. The ultraviolet and infrared spectra of these new class of heterocyclic compounds have been studied. The anti-bacterial and anti-fungal activities of these compounds have been reported.

INTRODUCTION

A NUMBER of naturally occurring as well as synthetic flavones were investigated for insecticidal properties.^{1,2} Introduction of a hydroxy group into the flavone nucleus was found to impart anthelmintic activity.³ 7-Amino-flavone was reported to possess anti-tubercular activity.⁴ 3'-Aminoflavone has spasmodic effect and is used in the treatment of angina pectoris.⁵ A number of N-substituted 8-amino-7-hydroxy chromones were investigated for anti-malarial properties⁶ and as central nervous system stimulants.⁷ Various condensed oxazoles exhibit appreciable bacteriostatic activity.⁸

Among the condensed flavones containing nitrogen or oxygen-nitrogen ring systems, only two compounds have so far been reported—one a flavono (6, 7) imidazole⁹ and the other a flavono (6, 7) oxazine.¹⁰ With a view to testing the anti-bacterial and anti-fungal activities, the synthesis of a few oxazolo-flavones has been undertaken. Compounds with an oxazole ring system in the 7, 8 positions of a flavone have not been so far reported in literature and they form a new class of condensed heterocyclic flavones. They may also be considered to be derivatives of 8-amino-7-hydroxy flavones, as also the nitrogen analogues of (7, 8) furanoflavones.

For the preparation of oxazolo-flavones, 7-hydroxy flavone has been synthesised by the modified 'Baker-Venkataraman transformation method'

starting from resacetophenone and benzoyl chloride using acetone and potassium carbonate.¹¹ Nitration¹² in sulphuric acid—nitric acid mixture yielded the 8-nitro derivative, which was subsequently reduced to the corresponding 8-amino compound by sodium dithionate.

Condensation of 8-amino-7-hydroxy flavone with acetic and propionic anhydrides yielded the 2'-methyl and 2'-ethyl oxazolo-flavones, by an analogous procedure to that adopted by Arndt¹³ for the preparation of coumarino (3, 4) oxazoles. The 2'-aryl analogues have been obtained by the condensation of 8-amino-7-hydroxy flavone with aromatic aldehydes in nitrobenzene medium.

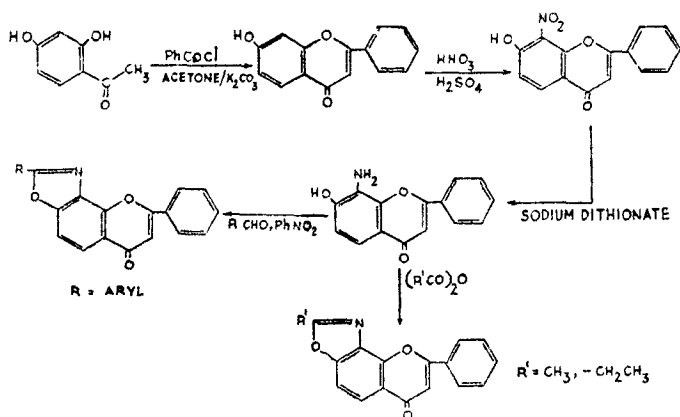


FIG. 1.

The oxazoles thus prepared have been included in Table I, together with their m.p., yields and percentage of nitrogen.

SPECTRA

The ultraviolet and infrared spectra of a few of the oxazolo-flavones have been recorded. In the ultraviolet region, all the oxazoles have exhibited a strong maximum in the band-II region around $255 \pm 15 \text{ m}\mu$ ($\log \epsilon 4.8$). The 7-hydroxy-8-amino flavone has shown a maximum at $263 \text{ m}\mu$ ($\log \epsilon 4.4$) with inflections at $327 \text{ m}\mu$ ($\log \epsilon 3.4$) and $333 \text{ m}\mu$ ($\log \epsilon 3.4$). In the case of 2'-aryl substituted oxazolo-flavones, an inflection at $370 \pm 15 \text{ m}\mu$ ($\log \epsilon 3.9$) has been obtained, in addition to the above band, which was not exhibited by the 2'-alkyl analogues (Table II).

In the infrared region, 7-hydroxy-8-amino flavone exhibits bands at 2.85μ (-OH group), 3.05μ (-NH₂ group) and 6.2μ (C=O group). In

the case of corresponding oxazoles, the first two bands are absent and the carbonyl band has been found to appear at $6.1\ \mu$, in addition to the bands due to the oxazole ring around $6.5\ \mu$, $7.5\ \mu$ and $9.2\ \mu$.

TABLE I

Compound	M.P. °C.	Yield %	Percentage of Nitrogen	
			Calculated	Found
1. 7-Hydroxy-8-amino flavone	140	35	5.6	5.5
2. 2'-Methyl	.. 228	60	5.0	5.3
3. 2'-Ethyl	.. 234	25	4.7	4.3
4. 2'-Phenyl	.. 271	80	4.1	3.9
5. 2'- <i>p</i> -Hydroxyphenyl	.. 252 <i>d</i>	15	3.9	3.8
6. 2'- <i>p</i> -Anisyl	.. 245 <i>d</i>	75	3.8	3.5
7. 2'-Vanillyl	.. 263 <i>d</i>	20	3.3	2.9
8. 2'-Piperonyl	.. 228	20	3.2	2.8
9. 2'- <i>p</i> -Chlorophenyl	.. 205	25	3.8	3.7
10. 2'- <i>p</i> -Dimethyl aminophenyl	.. 232	25	7.3	6.9
11. 2'-2,4-Dichlorophenyl	.. 223	15	3.2	2.9

PHYSIOLOGICAL ACTIVITY

The bacteriostatic activity has been determined by the tube dilution method using *S. aureus*, *B. coli* and *B. subtilis* as test organisms. All the compounds exhibited appreciable activity at 10,000 dilution but at 100,000 dilution, 2'-*p*-chlorophenyl and 2'-*p*-hydroxyphenyl compounds have shown activity.

The fungistatic activity has been determined by the radial growth measurement technique using *A. niger* as the test organism. All the compounds exhibited activity at 10,000 dilution, but the 2'-vanillyl substituted compound was appreciably active at 100,000 dilution (Table III).

TABLE II
Ultraviolet spectra

Compound	Band-II m μ	Log. ϵ	Band-I m μ	Log. ϵ
1. 7-Hydroxy-8-amino flavone	263	4.4	326-327 336	3.4 3.3
2. 2'-Phenyl-(7, 8)-oxazolo- flavone	260	4.6	375-376	3.9
3. 2'-Anisyl-(7, 8)-oxazolo- flavone	258	4.9	393-394	3.9
4. 2'-Methyl-(7, 8)-oxazolo- flavone	260	4.4
5. 2'-Ethyl-(7, 8)-oxazolo- flavone	255	4.8

EXPERIMENTAL

8-Amino-7-hydroxy flavone.—7-Hydroxy flavone (2.7 g.), sodium dithionate (8 g.), alcohol (15 ml.), water (30 ml.) and liquor ammonia (30 ml.) were refluxed for about half-an-hour, until a clear solution was obtained. Then it was neutralised with the dilute hydrochloric acid until the neutralisation point was reached. The product was filtered and recrystallised from ethanol, m.p. 140° C. Yield: 1.2 g. (40%).

General procedure for 2'-alkyl substituted oxazolo-flavones.—7-Hydroxy-8-amino flavone (1 g.) and the appropriate acid anhydride (15 ml.) were refluxed for half-an-hour and poured on crushed ice. The solid thus separated was filtered, washed thoroughly with water, and then recrystallised from ethanol.

General procedure for 2'-aryl substituted oxazolo-flavones.—7-Hydroxy-8-amino flavone (1 g.), an aromatic aldehyde (1.5 g.) and nitrobenzene (15 ml.) were refluxed for 3-4 hours. Nitrobenzene was removed by steam distillation. The residue that was left in the flask was filtered, washed with petroleum ether to remove any small amount of nitrobenzene present and then recrystallised from benzene-petroleum ether.

TABLE III
Physiological activity

Compound: (7, 8) Oxazolo-flavone	Bactereostatic activity						Fungistatic activity		
	B.C.		B.S.		S.A.		% inhibition		
	A	B	A	B	A	B	A	B	
1. 2'-Phenyl	..	-	±	-	±	±	+	50	39
2. 2'-Methyl	..	-	+	-	+	-	+	39	30
3. 2'-Ethyl	..	-	+	-	+	-	+	40	32
4. 2'- <i>p</i> -Anisyl	..	-	+	-	+	-	+	50	30
5. 2'-Dimethylamino-phenyl	..	-	+	-	+	±	+	61	39
6. 2'- <i>p</i> -Chlorophenyl	..	-	-	±	+	-	-	50	23
7. 2'- <i>p</i> -Hydroxyphenyl	..	-	-	-	-	-	+	80	41
8. 2'-2, 4-Dichlorophenyl	..	-	+	-	+	-	-	50	26
9. 2'-Vanillyl	..	-	±	-	±	-	±	73	57
10. 2'-Piperonyl	..	-	+	±	+	-	+	50	30
11. 7-Hydroxy-8-amino flavone	±	+	±	+	-	±		25	15

+ No activity; ± Partial; - Full activity. Concentration A: 1 Part in 10,000; Concentration B: 1 Part in 100,000.

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