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Synthesis, spectra and physiological activity of pyrono (2, 3-e) benzoxazoles

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ABSTRACT

A few 2-aryl and 2-heterocyclic substituted pyrono (2, 3-e) benzoxazoles have been synthesized by condensing 8-amino-7-hydroxy-2-methyl chromone with aromatic or heterocyclic carboxylic acids employing polyphosphoric acid as the condensing agent. The ultraviolet, infrared, NMR and mass spectra of these compounds have been presented. Antibacterial evaluation revealed that the 2-naphthyl and 2-(3-coumarinyl) derivatives exhibit considerable activity.

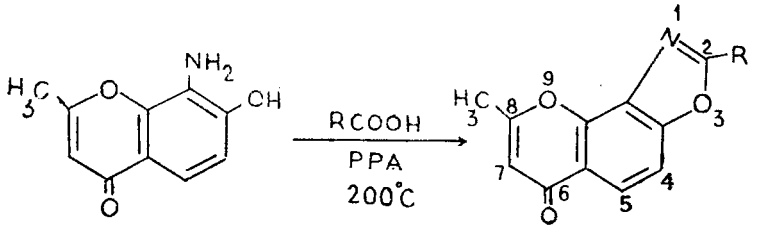
INTRODUCTION

INTEREST in the oxazolo pyran group of heterocycles was stimulated by the isolation of an oxazolo (3, 4-*d*) coumarin from the broad-spectrum antibiotic, Novobiocin.[1] The synthesis of a number of oxazolo α-pyrones, γ-pyrones, and their benzoderivatives followed, as analogues of this antibiotic, for evaluating their physiological properties.[2–5] A recent report[6] indicates that building up of an oxazoline nucleus on the antibiotic Gentamycin C_2 enhances its antibacterial properties.

From these laboratories, the synthesis and physiological activity of a few oxazolo (7, 8-*d*) and (6, 7-*d*) chromones have been reported by us in two earlier communications.[7, 8] The method adopted was to reflux the appropriate amino hydroxy chromones with an aromatic aldehyde in nitrobenzene medium. Although the yields were fairly good, this procedure not only involved purification of the products to remove the nitrobenzene, but also employment of an aldehyde. Since naphthoic and heterocyclic carboxylic acids are more easily accessible than the corresponding aldehydes, the feasibility of utilising the acids for preparing the oxazoles has been explored. The present work describes the results of these investigations.

It was earlier recorded in literature[9] that polyphosphoric acid could be used for cyclizations involving acids and their derivatives, when treated with

o-phenylenediamines, *o*-amino phenols and *o*-amino thiophenols. The yields were reported to be quantitative. Hence, this reagent was chosen as the cyclizing agent for the condensation of acids with 2-methyl-8-amino-7-hydroxy chromone (Chart I). The acids made use of in the condensation include *o*- and *p*-toluic acids, *o*-anisic acid, α- and β-naphthoic acids, coumarin-3-carboxylic acid and its 6-chloro, 6-bromo and 6-methyl analogues and nicotinic acid. The reactions were carried out at elevated temperatures (for details, *see* experimental section) and in the case of coumarin acids, longer duration was found to be necessary. The resulting 6H-pyrano (2, 3-*e*) benzoxazol-6-ones (more commonly termed oxazolo (7, 8-*d* chromones) have been included in table 1.



I Chart I II

Fitton and Hatton[10] earlier reported the synthesis of 2-alkyl pyrano (2, 3-*e*) benzoxazol-6-ones by treating a few amino hydroxy chromones with acetic anhydride and heating the resulting N, O-diacetate for effecting cyclization. They also made use of the azides, resulting from diazotised amino hydroxy chromones and sodium azide, for condensation with aliphatic acids employing polyphosphoric acid. In our investigation, it was observed that the amines could be directly employed without conversion into azides. Barker and Ellis[11] also synthesized a few 2-aryl-pyrano (2, 3-*e*) benzoxazol-6-ones by treating 7-amino-8-hydroxy chromones with aromatic aldehydes and cyclising the resulting Schiff bases by dehydrogenation with lead tetra acetate. Although the yields reported were good this method also, utilises the less readily accessible aldehydes. Hence, our method employing carboxylic acids and polyphosphoric acid as condensing agent is the simplest for preparing pyrano benzoxazoles and the products found to be pure and high in yields.

Spectral characteristics of pyrano (2, 3-*e*) *benzoxazoles*

Ultraviolet spectra.—All the title compounds exhibited three main regions of absorption, around 220±5 nm, 250±10 nm and 290±4 nm. The first and the last are attributable to the chromone ring, in analogy with the absorption data of 2-methyl chromone[12] which absorbs at 225 nm and 295 nm. The middle band is analogous to that of 2-phenyl oxazole[12] which exhibits

Table 1

Sl. No.	Pyrano (2, 3-e) benzoxazoles	M.P. ° C	Yield %	Calculated C	Calculated H	Calculated N	Found C	Found H	Found N	Solvent	λ max (nm)	log ε
1.	2-*p*-toluyl	257–58	76	74·2	4·5	4·8	74·5	4·6	5·0	Benzene	303 (shoulder), 293, 264, 224	4·5, 4·5, 4·5, 4·5.
2.	2-*o*-toluyl	189–90	79	74·2	4·5	4·8	74·5	4·4	4·6	Benzene-petroleum ether	315 (shoulder), 288, 260, 219.	4·1, 4·5, 4·6, 4·5.
3.	2-*o*-methoxy	241–42	9	70·4	4·2	4·6	70·1	4·0	4·8	Benzene	321, 291, 262, 223.	4·4, 4·5, 4·6, 4·7.
4.	2-(2-naphthyl)	260–61	85	77·1	4·0	4·3	77·3	3·7	4·0	Benzene	315, 276, 257 226.	4·6, 4·6, 4·8, 4·6.
5.	2-(1-naphthyl)	200–01	77	77·1	4·0	4·3	77·4	3·8	4·5	Benzene	333, 320, 240, 222.	4·4, 4·4, 4·6, 4·7.
6.	2-(3-coumarinyl)	289–90	76	69·6	3·2	4·1	69·8	3·0	4·3	Aqueous dioxane	351, 333, 290, 244, 238.	4·5, 4·5, 4·3, 4·6, 4·6.
7.	2-(6-bromo-3-coumarinyl)	305–06	77	56·6	2·4	3·3	56·4	2·2	3·1	Aqueous dioxane	356, 320, 303, 289, 229.	4·5, 4·5, 4·5, 4·5, 4·9.
8.	2-(6-chloro-3-coumarinyl)	316–17	73	63·2	2·6	3·7	63·1	2·4	3·4	Aqueous dioxane	358, 319, 288, 245, 227.	4·4, 4·3, 4·2, 4·5, 4·7.
9.	2-(6-methyl-3-coumarinyl)	278–79	73	70·2	3·6	3·9	70·5	3·9	4·2	Benzene	358, 323, 291, 245, 225.	4·3, 4·2, 4·1, 4·3 4·6
10.	2-(3-pyridyl)	267–68	67	69·1	3·6	10·1	69·1	3·5	10·3	Benzene	316, 304, 292, 258, 224.	4·2, 4·5, 4·5, 4·6 4·6.

a single maximum at 263 nm. In addition, all the compounds exhibited a shoulder around 310±10 nm, which is characteristic of the benzoxazole system. In the case of 2-coumarinyl derivatives, an additional band was noticed around 354 ± 4 nm, which must be due to the following extended conjugation (Chart II).

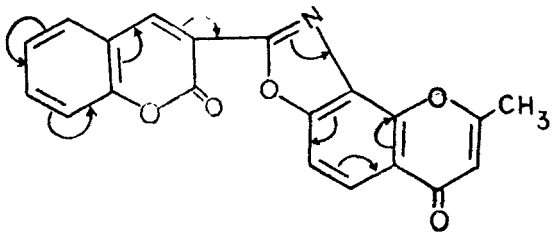


Chart II

Diphenyl polyenes of the type Ph-(CH = CH)$_n$ Ph were reported[13] to absorb around 350 nm when $n = 2$ and the above chromophoric system is analogous.

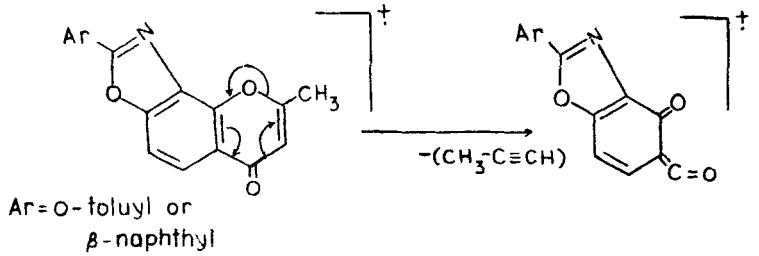


Chart III

Infrared spectra : All the pyrano benzoxazoles exhibited a strong band around 1650 cm^{-1}, characteristic of the chromone carbonyl group. In the case of 2-coumarinyl derivatives, the lactone carbonyl was also found to merge with this band. Bands around 1550 cm^{-1} for the $>C=N$, 1075 cm^{-1} for C–O–C and 825 cm^{-1} for the $>C=C<$ have also been recorded.

NMR spectra : The protons of the chromone 8-methyl group reveal themselves at 2·5 δ, and the ethylenic proton at the 7-position (*see* Chart I for numbering) at 6·2 δ. The two aryl protons at 4, 5-positions were indicated by signals at 8·1 δ and 8·3 δ with a coupling constant of about 15 cps, confirming their position ortho to each other. In the case of the 2-coumarinyl derivatives the coumarin proton at the 4-position was recorded around 9·2 δ. The other 2-aryl derivatives gave signals for these protons between 7·2–7·6 δ.

Mass spectra : The mass spectra of 2-*o*-toluyl-8-methyl-pyrano (2, 3-*e*) benzoxazol-6-one and its 2-β-naphthyl analogue were recorded on a CED 21–110B mass spectrometer (table 2) and the fragmentation pattern is included in Chart III. The molecular ion peaks are the base peaks in either case and very little fragmentation has been observed, indicating the high stability of this system to electron impact. Barker and Ellis[11] earlier observed that with 2-nitro aryl-8-carbethoxypyrano (2, 3-*e*) benzoxazol-6-one, the nitro and carbethoxy groups were cleaved prior to ring cleavage. Moreover the usual retro-Diels-Alder fission of the chromone system[14] was not observed by these workers in their series. However, the major fragmentation in the present series has been only through such loss of carbon monoxide from the molecular ion and was also found to be a minor fragmentation process. Ions corresponding to $ArCN^+$ were also recorded in the spectra.

Physiological activity : The antibacterial activity of all the title compounds has been evaluated employing the tube dilution method[15] with *S. aureus, B. coli and B. subtilis* as the test organisms. The 2-α-naphthyl 2-β-naphthyl, and 2-(3-coumarinyl) analogues inhibited the growth of all the three bacteria at 10 ppm concentration. The others were active only at 100 ppm.

EXPERIMENTAL

Preparation of pyrano (2, 3-e) *benzoxazol-6-ones*

8-Amino-7-hydroxy-2-methyl chromone (0·01 mole) and the appropriate acid (0·01 mole) were heated with phosphorous pentoxide (15 g) and ortho-

Table 2

Compound 2

m/e	292	291	290	262	263	251	223	167	166	145·5
% I	21·0	100	8·4	1·4	1·4	5·6	8·4	2·8	2·8	1·4
m/e	140	139	119	117	102	91	90	89	78	77
% I	1·4	1·4	4·2	7·0	2·8	7·0	5·6	5·6	2·8	4·2
m/e	76	63	50	43	39					
% I	2·8	2·8	2·8	2·8	5·6					

Compound 4

m/e	328	327	299	298	288	287	204	203	202	164
% I	22·9	100	2·5	2·5	2·5	11·9	2·5	17·9	5·1	4·2
m/e	153	143·5	127	126	106	89	78	77	76	75
% I	18·7	3·4	21·3	7·6	4·3	3·4	5·9	4·3	3·4	3·4
m/e	53	51	50	43	39	38				
% I	2·5	2·5	3·4	3·4	4·3	2·5				

phosphoric acid (10 ml) first at 150–60° C for an hour and half and then at 200–205° C for a further period of three hours. In the case of coumarin 3-carboxylic acids, heating at the higher temperature was continued for about 4 hours. The mixture was poured over ice-cold water and the resulting solid washed with sodium bicarbonate. Recrystallization was effected with the appropriate solvent as indicated in table 1.

Measurement of spectra

The ultraviolet spectra were recorded on a Beckmann DK-2A spectrophotometer at a concentration of 10^{-3} molar.

The I.R. spectra were recorded on a Perkin-Elmer 137 spectrophotometer in nujol mulls.

The NMR spectra were recorded in deuterated chloroform solution in a Varian A-60 spectrometer.

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REFERENCES

1. Hinman, J. W., Caron, E. L. and Hocksema, H., *J. Am. Chem. Soc.* **79** 3789 (1957).
2. Stammer, C. H., *J. Org. Chem.* **25** 460 (1960).
3. Okumura, K., *Yakugaku Zasshi* **81** 307 (1961).
4. Dallacker, F., Kratzer, P. and Lipp, M., *Ann.* **643** 97 (1961).
5. Rao, K. S. R. K. M. and Rao, N. V. S., *Proc. Indian Acad. Sci.* **67** 42 (1969).
6. Cooper, D. J., Weinstein, J. and Waitz, J. A., *J. med. Chem.* **14** 1118 (1971).
7. Reddy, Y. D. and Somayajulu, V. V., *Proc. Indian Acad. Sci.* **74** 265 (1971).
8. Reddy, Y. D. and Somayajulu, V. V., *Proc. Indian Acad. Sci.* **76** 263 (1972).
9. Hein, D. W., Alheim, R. J. and Leavitt, J. J., *J. Am. Chem. Soc.* **79** 427 (1957).
10. Fitton, A. O. and Hatton, B. T., *J. Chem. Soc. C.* 2518 (1970).
11. Barker, G. and Ellis, G. P., *J. Chem. Soc. C.* 1482 (1971).
12. Armarego, W. L. F., In *Physical Methods in Heterocyclic Chemistry*, Vol. III, p. 193, Ed. by Katritzky, A. R., Academic Press (New York) (1971).
13. Fieser, L. F. and Fieser, M., In *Organic Chemistry*, Reinhold (New York), p. 881 (1958).
4. Djerassi, C., Budzikiewiz, H. and Williams, D. H., In *Mass Spectrometry of Organic Molecules*, p. 209, Holden-Day (San Francisco) (1964).
15. Morley, J., *J. Path. Bact.* **57** 379 (1945).