SEARCH FOR PHYSIOLOGICALLY ACTIVE COMPOUNDS

Part XXIII. Synthesis of 3-(3-Pyridyl) and 3-(3-Pyridyl)-4-Methyl Coumarins

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Abstract

A number of 3-(3-pyridyl) coumarins with and without 4-methyl substituent have been prepared following Oglialoro and modified Perkin reactions. These compounds have been tested against fish and bacteria. Of all the compounds tested, 7-bromo-4-methyl-3-(3-pyridyl) coumarin exhibited maximum activity. A few have also shown bacteriostatic activity.

Introduction

Recent work from these laboratories[1] showed that the replacement of the side phenyl substituent by a furyl substituent at 3-position, improved the fish toxicity of the coumarin molecule. Since 3-substituted pyridines like nicotine, nornicotine and anabasine are known to be highly insecticidal,[2] it was considered desirable to investigate as to whether a coumarin with its 3-position linked to the 3-position of pyridine would result in a compound with enhanced activity.

Moffett,[3] Bhandari[4] and recently Buu-Hoi[5] synthesized a few 3-(3-pyridyl) coumarins and reported them to exhibit central nervous system stimulant activity,[3] antifungal activity[3] and to function as spasmolytic[5] and uricosuric agents.[5] None of these reports describe any insecticidal or bacteriostatic properties of 3-(3-pyridyl) coumarins.

In the present investigation, twenty new 3-(3-pyridyl) coumarins (I) have been synthesized by following two general methods (Fig. 1). The first method (A) involves the condensation of substituted salicylaldehydes with sodium 3-pyridyl acetate and acetic anhydride under Oglialoro reaction[6] conditions. This method was not found to be satisfactory as the reaction often gave gums requiring extensive purification and the yields never exceeded 30-40%. The alternative method, modified Perkin reaction (Method-B),

adopted by Moffett involves the heating of the respective salicylaldehydes or *o*-hydroxy acetophenones with 3-pyridylacetic acid and acetic anhydride in the presence of a small quantity of triethylamine. The products obtained in this reaction are clean and the yields have been uniformly good.

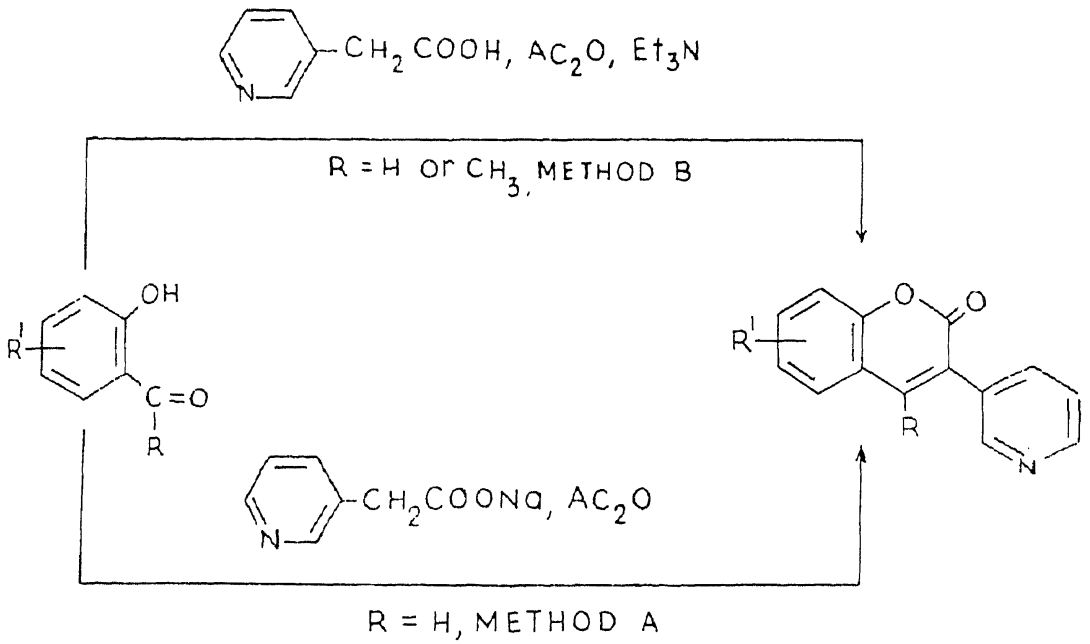

FIG. 1

The 7-hydroxy-3-(3-pyridyl) coumarin has been prepared following Buu-Hoi's acrylonitrile procedure[5] for the purpose of comparison with the one obtained by the hydrolysis of the 7-acetoxy-3-(3-pyridyl) coumarin following Moffett's procedure. The 8-hydroxy-3-(3-pyridyl) coumarin has been obtained by demethylating the 8-methoxy derivative with pyridine hydrochloride. The 7-amino-3-(3-pyridyl) coumarin is prepared by reducing the nitro derivative with iron and acetic acid. All the 3-(3-pyridyl) coumarins prepared are listed in Table I with their melting points, yields and analytical data.

Fish toxicity.—It can be seen from the fish toxicity data (Table II) that the introduction of a side pyridyl substituent confers greater activity on the coumarin molecule than a side phenyl[7] or furyl[1] substituent. A methoxyl in 7-position of 3-(3-pyridyl) coumarin is found to enhance the activity. Among the compounds tested against the freshwater fish (*barbus ticto*), 7-bromo-4-methyl-3-(3-pyridyl) coumarin has the maximum activity so far observed in the synthetic oxygen heterocycles and is half as active as rotenone, the well-known natural insecticide.[8]

Bacteriostatic activity.—Of all the compounds tested on bacteria (Table II), 6-bromo-3-(3-pyridyl), 6, 7- and 8-nitro-3-(3-pyridyl) and 7-bromo and 7-chloro-4-methyl-3-(3-pyridyl) coumarins have shown very good activity against *Staphylococcus aureus*, *Bacillus subtilis* and *Bacillus coli* at 100 ppm. The nitro coumarins and the 7-chloro-4-methyl coumarins are partially active even at 10 ppm on *Staphylococcus aureus* and *Bacillus coli.*

EXPERIMENTAL

Melting points were taken in a sulphuric acid bath and are uncorrected.

Procedure for the synthesis of 3-(3-*pyridyl*) *coumarins adopting Oglialoro's* (*Method-A*).—A mixture of salicylaldehyde (0·02 mole), fused sodium 3-pyridyl acetate (0·04 mole) and acetic anhydride (0·5 mole) was refluxed at 150-60° C in an oil bath for twenty-four hours. It was then poured on crushed ice and left overnight. The pasty mass that settled down was separated and triturated with small amount of cold alcohol. The solid thus separated was filtered and recrystallised from a suitable solvent.

Procedure of modified Perkin reaction (*Method-B*).—To a mixture of salicylaldehyde (0·02 mole), 3-pyridyl acetic acid (0·025 mole) and acetic anhydride (0·5 mole) was added triethylamine (2 ml). The mixture was then refluxed in an oil bath for three hours at 150-60° C. It was poured into ice-water with stirring and the solid that separated was filtered, washed with water and recrystallised from a suitable solvent. 3-(3-pyridyl)-4-methyl coumarins have been prepared by using *o*-hydroxy acetophenones in place of salicylaldehydes in the above procedure.

Deacetylation of 7-*acetoxy* 3-(3-*pyridyl*) *coumarin.*—After refluxing the mixture of acetoxy coumarin (1·5 g), methanol (150 ml) and 15% aqueous hydrochloric acid (70 ml) on a water bath for two hours and removing the methanol, the coumarin hydrochloride separated as dense light yellow solid. It was recrystallised from water. The hydrochloride (1·5 g) was dissolved in 10% sodium hydroxide solution (75 ml) and neutralised with acetic acid. The precipitate obtained was filtered and recrystallised from aqueous acetic acid.

Demethylation of methoxy coumarins.—A mixture of methoxy-3-(3-pyridyl) coumarin (1 g) and freshly distilled pyridine hydrochloride (4 g) was heated under reflux for twenty minutes, cooled and treated with water. The residual crystalline mass was recrystallised from aqueous acetic acid.

TABLE I

3-(3-Pyridyl) coumarins

Sl. No.	3-(3-Pyridyl) coumarin	M.P. (°C)	Yield (%)	Solvent	Mol. Formula	Analysis (%) Calculated C	H	N	Found C	H	N
1.	6-Nitro ..	254	91	HOAc	$C_{14}H_8N_2O_4$	62·69	3·00	10·45	62·54	3·10	10·61
2.	6-Chloro ..	213	80	CH_3COCH_3	$C_{14}H_8ClNO_2$	65·22	3·10	5·43	65·48	3·14	5·39
3.	7-Acetoxy ..	176	78	CH_3COCH_3	$C_{16}H_{11}NO_4$	68·82	3·94	4·98	68·67	4·01	4·81
4.	7-Methoxy ..	188	58	CH_3COCH_3	$C_{15}H_{11}NO_3$	71·15	4·35	5·53	71·25	4·34	5·54
5.	7-Nitro ..	251	60	HOAc	$C_{14}H_8N_2O_4$	62·69	3·00	10·45	62·84	2·95	10·34
6.	7-Amino ..	246	52	EtOAc	$C_{14}H_{10}N_2O_2$	70·55	4·20	11·77	70·41	4·19	11·88
7.	8-Methoxy ..	175	52	CH_3COCH_3	$C_{15}H_{11}NO_3$	71·15	4·35	5·53	71·25	4·30	5·42
8.	8-Nitro ..	215	51	HOAc	$C_{14}H_8N_2O_4$	62·69	3·00	10·45	62·52	3·05	10·60
9.	8-Methoxy-6-nitro ..	210	64	MeOH	$C_{15}H_{10}N_2O_5$	60·40	3·36	9·40	60·88	3·31	9·59
10.	8-Hydroxy-6-nitro ..	300	61	aq. HOAc	$C_{14}H_8N_2O_5$	59·16	2·82	9·86	59·35	2·82	9·68

11. 8–Methoxy–6–bromo	..	200	68	CH_3COCH_3 / MeOH	$C_{15}H_{10}BrNO_3$	54·22	3·01	4·22	54·43	3·08	4·28
12. 8–Hydroxy–6–bromo	..	300	81	aq. HOAc	$C_{14}H_8BrNO_3$	52·83	2·52	4·40	52·81	2·60	4·44
13. 6, 8–Dichloro	..	213	71	CH_3COCH_3 / MeOH	$C_{14}H_7Cl_2NO_2$	57·83	2·40	4·78	57·81	2·42	4·78
14. 6, 8–Dibromo	..	217	60	MeOH	$C_{14}H_7Br_2NO_2$	44·10	1·84	3·68	44·34	1·85	3·70
15. 8–Nitro–6–bromo	..	168	53	aq. HOAc	$C_{14}H_7BrN_2O_4$	48·42	2·02	8·11	48·30	2·01	8·21
16. 8–Bromo–6–nitro	..	179	58	CH_3COCH_3 / MeOH	$C_{14}H_7BrN_2O_4$	48·42	2·02	8·11	48·54	2·00	8·12
17. 5, 6–Benzo	..	236	78	CH_3COCH_3	$C_{18}H_{11}NO_2$	79·12	4·03	5·13	79·21	4·00	5·37
18. 7–Acetoxy–4–methyl	..	170	80	EtOH	$C_{17}H_{13}NO_4$	69·15	4·44	4·72	69·30	4·48	4·81
19. 7–Chloro–4–methyl		183	66	EtOH	$C_{14}H_{10}ClNO_2$	66·18	3·68	5·15	66·00	3·64	5·14
20. 7–Bromo–4–methyl	..	170	60	EtOH	$C_{14}H_{10}BrNO_2$	56·97	3·16	4·43	56·89	3·16	4·40

TABLE II

Fish toxicity and bacteriostatic Activity Data of 3-(3-Pyridyl) coumarins

Sl. No.	3-(3-Pyridyl) coumarin	Fish toxicity 20 ppm turning time in minutes	Bacteriostatic activity					
			S.A.		B.S.		B.C.	
			A	B	A	B	A	B
1.	Simple[4] ..	7·0	+	..	+	..	±	+
2.	6-Nitro ..	Not active in 24 hours	−	±	−	+	−	±
3.	6-Chloro ..	20·0	−	±	+	..	−	±
4.	6-Bromo[3] ..	16·0	−	+	−	+	−	±
5.	7-Hydroxy[5] ..	5·7	±	+	−	±	+	..
6.	7-Methoxy ..	1·3	+	..	+	..	+	..
7.	7-Nitro ..	Not active in 24 hours	−	±	−	+	−	±
8.	7-Amino ..	10·0	−	+	+	..	−	+
9.	8-Hydroxy[5] ..	8·0	−	±	−	+	+	..
10.	8-Methoxy ..	1·5	+	..	+	..	+	..
11.	8-Nitro ..	Not active in 24 hours	−	±	−	+	−	±
12.	8-Methoxy-6-nitro	do.	+	..	+	..	+	..
13.	8-Hydroxy-6-nitro	do.	+	..	+	..	+	..
14.	8-Methoxy-6-bromo	do.	+	..	+	..	+	..
15.	8-Hydroxy-6-bromo	do.	+	..	+	..	+	..
16.	8-Nitro-6-bromo	Not active in 24 hours	+	..	+	..	+	..
17.	8-Bromo-6-nitro ..	do.	+	..	+	..	+	..
18.	6, 8-Dichloro ..	40·0	+	..	±	+	±	+
19.	6, 8-Dibromo ..	35·5	+	..	±	+	±	+
20.	5, 6-Benzo ..	Not active in 24 hours	+	..	+	..	+	..
21.	7-Hydroxy-4-methyl[5]	4·1	−	+	±	+	±	+
22.	7-Methoxy-4-methyl[5]	1·2	±	+	+	..	±	+
23.	7-Chloro-4-methyl	1·1	−	±	−	±	−	±
24.	7-Bromo-4-methyl	0·6	−	±	−	+	−	±

S.A. = *Staphylococcus aureus*, B.S. = *Bacillus subtilis*, B.C. = *Bacillus coli*

\+ = Full growth, ± = Partial growth, − = No growth.

A = 100 ppm., B = 10 ppm.

7-Amino-3-(3-pyridyl) coumarin.—To the boiling solution of acetic acid and 7-nitro-3-(3-pyridyl) coumarin (2 g) was added iron filings (3 g) in small lots so that the reaction may not become too vigorous. After the addition was complete, the reaction mixture was refluxed for two hours and allowed to stand overnight. The ferric acetate that settled down was filtered off and the filtrate concentrated to half the bulk and cooled, when a further quantity of ferric acetate separated which was again filtered. Finally, the filtrate was concentrated to 15 ml and poured in water. It was extracted with ether and the etherial layer was evaporated after washing with sodium bicarbonate solution. The solid residue was recrystallised from ethyl acetate as bright yellow needles.

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