SEARCH FOR PHYSIOLOGICALLY ACTIVE COMPOUNDS

Part XXVI. Synthesis of Amino and Halo Substituted 4-Hydroxy-3-phenylcoumarins and Isoflavones

B. SREENIVASULU, V. SUNDARAMURTHY AND N. V. SUBBA RAO, F.A.Sc.

(Department of Chemistry, Osmania University, Hyderabad 500007)

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ABSTRACT

A few 4-hydroxy-3-phenylcoumarins have been synthesised from 2-hydroxy deoxybenzoins by condensing them with diethyl carbonate in the presence of sodium. By the reaction of the same deoxybenzoins with ethylorthoformate in the presence of pyridine and piperidine a few isoflavones have also been prepared. The bacteriostatic and fish-toxic properties of these compounds have been evaluated.

ISOFLAVONES and 3-arylcoumarins occur together in plants and have been postulated to arise from a common biogenetic precursor[1,2]. While 3-aryl-4-hydroxycoumarins exhibit anticoagulant and analgesic[3], hypotensive and spasmolytic[4] activities, the isoflavones are known to possess oestrogenic, fish-toxic insecticidal and antifungal[5] properties. Subba Rao and coworkers[6,7] have reported that a halogen substituent stepped up the fish-toxicity and that an amino substituent contributed to the antibacterial activity of the coumarins and chromones. The present paper deals with the synthesis of amino and halo-4-hydroxycoumarins and isoflavones.

Except for the reported synthesis of 6-bromo-4-hydroxy-3-phenyl coumarin[8] by the intramolecular cyclisation of methyl 5-bromo-2-phenyl acetyl salicylate and 7-chloro isoflavone[9] by the condensation of 4-chloro-2-hydroxy deoxybezoin with ethoxalyl chloride, there seems to be no other reference available on the synthesis of halo and amino-4-hydroxy-3-phenyl-coumarins and isoflavones.

We have prepared, deoxybenzoins having acetamino and halo substituents at 4 and 5-positions by the Friedel-Crafts acylation of phenyl acetyl-chloride on acetyl *m*-anisidine[10] and acetyl *p*-anisidine respectively. The 4-chloro[9], 5-chloro, 4-bromo and 5-bromo-2-hydroxy deoxybenzoins were prepared by the Fries migration of the phenylacetyl derivatives of the respective phenols. 5-chloro deoxybenzoin has earlier been prepared by Kindler

Table 1. *2-Hydroxy deoxybenzoins*

2-Hydroxy deoxy-benzoin	m.p. (°C)	Molecular formula	Analysis			
			Found		Required	
			C	H	C	H
5-Acetamino	142	$C_{16}H_{15}NO_3$	71·61	5·72	71·31	5·65
5-Bromo	70	$C_{14}H_{11}BrO_2$	57·81	3·73	57·73	3·81
4-Bromo	68	$C_{14}H_{11}BrO_2$	57·63	3·89	57·73	3·81

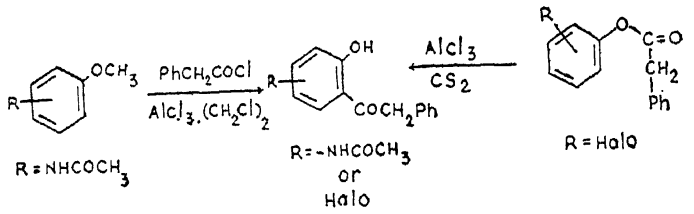

FIG. 1

and Oelsläger[11] by heating a mixture of *p*-chlorophenol, phenylacetic acid and BF_3 in a sealed tube.

The acetamino and halo deoxybenzoins thus prepared, on condensation with diethylcarbonate in the presence of sodium[12] gave the corresponding 4-hydroxy-3-phenylcoumarins. Following this procedure, 7-acetamino, 7-chloro, 7-bromo, 6-acetamino, 6-chloro and 6-bromo-4-hydroxy-3-phenyl coumarins have been prepared and are listed in table 2. The 7 and 6-amino compounds could be obtained from the corresponding acetamino derivatives by deacetylation using concentrated hydrochloric acid.

The acetamino and halo isoflavones have been prepared by the reaction of the respective deoxybenzoins with ethylorthoformate in the presence of pyridine and piperidine. The acetamino isoflavones have been deacetylated to the corresponding amino derivatives using methanolic hydrogen chloride.

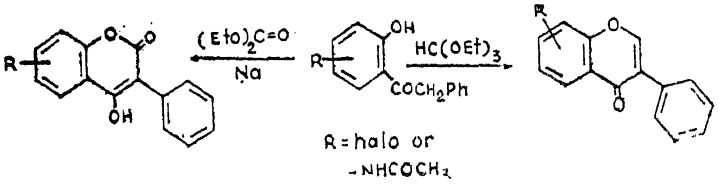

FIG. 2

Table 2. *4-Hydroxy-3-phenylcoumarins*

4-Hydroxy-3-phenyl coumarin	m.p. (°C)	Solvent	Molecular formula	Analysis			
				Found		Required	
				C	H	C	H
7-Acetamino	265	HOAc	$C_{17}H_{13}NO_4$	69·38	4·40	69·15	4·44
7-Amino	254	HOAc	$C_{15}H_{11}NO_3$	70·81	4·47	71·15	4·34
7-Chloro	257	EtOH	$C_{15}H_9ClO_3$	66·21	3·36	66·06	3·33
7-Bromo	262	EtOH	$C_{15}H_9BrO_3$	56·69	2·92	56·81	2·86
6-Acetamino	274	EtOAc	$C_{17}H_{13}NO_4$	69·41	4·46	69·15	4·44
6-Amino	242	HOAc	$C_{15}H_{11}NO_3$	71·32	4·44	71·15	4·34
6-Chloro	250	EtOAc	$C_{15}H_9ClO_3$	66·38	3·34	66·06	3·33

Table 3. *Isoflavones*

Isoflavone	m.p. (°C)	Solvent	Molecular formula	Analysis			
				Found		Required	
				C	H	C	H
7-Acetamino	206	HOAc	$C_{17}H_{13}NO_3$	73·11	4·51	73·48	4·66
7-Amino	160	MeOH	$C_{15}H_{11}NO_2$	76·13	4·53	75·97	4·64
7-Chloro*	150	MeOH	$C_{15}H_9ClO_2$	70·48	3·51	70·19	3·53
7-Bromo	160	EtOH	$C_{15}H_9BrO_2$	59·67	3·10	59·80	3·00
6-Acetamino	268	MeOH	$C_{17}H_{13}NO_3$	73·18	4·62	73·48	4·66
6-Amino	189	MeOH	$C_{15}H_{11}NO_2$	75·84	4·61	75·97	4·64
6-Chloro	179	MeOH	$C_{15}H_9ClO_2$	70·40	3·62	70·19	3·53
6-Bromo	170	EtOH	$C_{15}H_9BrO_2$	59·69	3·09	59·80	3·00

* Prepared from 7–Amino-isoflavone.

The 7-chloro isoflavone prepared from 7-amino isoflavone by diazotization and Sandmeyer reaction was identical in all respects with the one obtained by direct condensation[9].

The UV and IR spectral properties of the 4-hydroxy-3-phenylcoumarins and isoflavones synthesized agree with those reported in literature[13,14].

Of all the compounds tested, amino and halo isoflavones show appreciable bacteriostatic activity against *Bacillus coli, Bacillus subtilis* and *Staphylococcus aureas.* Though the amino isoflavones showed some activity against fish, the halo isoflavones were surprisingly inactive.

EXPERIMENTAL

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

General Procedure for the preparation of acetamino-2-hydroxy deoxybenzoins.

Powdered aluminium chloride (42 g) was added slowly with shaking and cooling to a mixture of acetyl-*p*- or *m*-anisidine (16·5 g) and phenyl acetyl chloride (33 g) in dichloroethane (40 ml) and the mixture refluxed for 2 hr. The reaction product was worked out following the procedure of Julia *et al*[10].

Halo deoxybenzoins

A mixture of halophenol (25·8 g) and phenyl acetyl-chloride (31 g) in benzene (100 ml) was refluxed on a water bath for 2·5 hr. The mixture was washed with sodium bicarbonate solution and water and the halophenol acetate was collected at its boiling point. The ester (43 g), aluminium chloride (29·3 g) and carbon disulphide (250 ml) were stirred for 1 hr. Rest of the procedure followed was same as adopted by Bryan *et al*[9].

Conversion of 7-amino isoflavone into 7-chloro isoflavone

7-Amino-isoflavone (0·6 g) was converted to 7-chloro isoflavone under Sandmeyer's reaction conditions. Yield (0·48 g; 60%), m.p. 150° (lit. m.p. 150°).

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REFERENCES

1. Subba Rao, N. V., *Advancing Frontiers in the Chemistry of Natural Products* (Hindusthan Publishing Corporation, Delhi) p. 110 (1965).
2. Ollis, W. D., New structural variants among the isoflavonoid and neoflavonoid classes. In *Recent Advances in Phytochemistry*, ed. T. J. Mebry (Associate eds. R. E. Alston of V. C. Runeckles), (Appleton-Century-Crafts, New York) **1** 329 (1968).
3. Van Zanten, B. and Nauta, W. T., *Arzneimittel-Forsch.* **14** 29 (1964).
4. Eugene, B., Darius, M. and Louis, F., *Chem. Abstr.* **72** 31615 (1970).
5. Biggers, *The Pharmacology of Plant Phenolics*, ed Fairburn (Academic Press, New York) p. 51 (1959).
6. Sundaramurthy, V. and Subba Rao, N. V., *Proc. Indian Acad. Sci.* **54A** 321 (1961).
7. Vijayalakshmi, M. and Subba Rao, N. V., *Curr. Sci.* **41** 680 (1972).
8. Huebner, C. F. and Link, K. P., *J. Amer. Chem. Soc.* **66** 656 (1944).
9. Bryan, J. D., Goldberg, A. A. and Wragg, A. W., *J. Chem. Soc.*, p. 1281 (1960).
10. Julia, M. and Baillarge, M., *Bull. Soc. Chim. (France)* p. 639 (1952).
11. Kindler, K. and Oelschläger, H., *Chem. Ber.* **87** 194 (1954).
12. Boyd, J. and Robertson, A., *J. Chem Soc.*, p. 174 (1948).
13. Lalitha, V. R. and Subba Rao, N. V., *Proc. Indian Acad. Sci.* **77** 157 (1973).
14. Dean, F. M., *Naturally Occurring Oxygen Ring Compounds* (Butterworths, London) p. 370 (1963)