Chemistry of Natural Compounds, Vol. 30, No. 2, 1994

SYNTHETIC AND MODIFIED ISOFLAVONES. VIII. NEW ANALOGS OF DERRUSNIN

A. Aitmambetov* and V. P. Khilya†

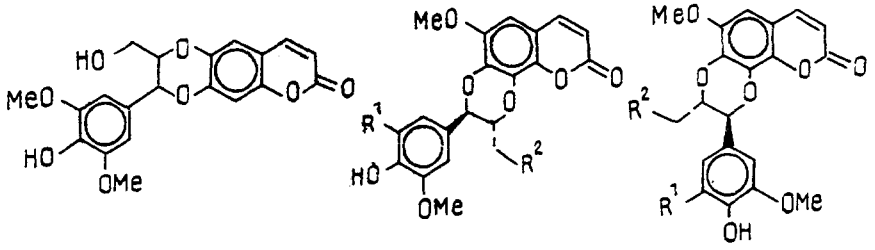
UDC 547.814.5

Derivatives of derrusnin and also its benzodioxane and benzodioxepane analogs have been synthesized. The structures of the compounds obtained have been confirmed by spectral studies.

Interest in coumarins and coumarinolignans is due to the wide practical use of these compounds. Coumarins are widely employed as fluorescent bleaches, dyes, and markers in the textile, polymer, printing, and photographic industries, among others [2].

It is known that many coumarins isolated from plant raw material contain a benzodioxolane fragment. Thus, for example, the molecule of 3-(1,3-benzodioxolan-5-yl)-4,5,7-trihydroxycoumarin (derrusnin) [3], isolated from the plant *Derris robusta* contains a 1,3-benzodioxolane system.

Coumarinolignans form a new class of natural compounds [4]. In terms of their chemical structure, they are condensed bicyclic systems consisting of coumarin and 1,4-benzodioxane nuclei.



Molluccanin

Cleomiscosin A (R^1=H, R^2=OH)

Cleomiscosin C (R^1=OMe, R^2=OH)

Cleomiscosin B (R^1=H, R^2=OH)

Cleomiscosin D (R^1=OMe, R^2=OH)

Coumarins and their condensed analogs of plant origin (molluccanin, cleomiscosins A, B, C,and D) [5-8] possess various types of biological action [6, 9-11]. Extracts containing cleomiscosin A are used in folk medicine as antipyretics an antispasmodics [5, 6].

In view of the above-mentioned useful properties of natural coumarins and coumarinolignans, it may be assumed that the combination in one molecule of coumarin and benzodioxolane, benzodioxane, or benzodioxepane nuclei would enable synthetic analogs of derrusnin with new biological properties to be obtained.

As the initial compounds for the synthesis of the 3-hetaryl-4-hydroxycoumarins we used the α-hetaryl-2-hydroxyacetophenones (**1a-c, 2b-d**) [12-14] containing 1,3-benzodioxolane, 1,4-benzodioxane, and 1,5-benzodioxepane nuclei.

The conversion of ketones (**1-2**) into the corresponding 3-hetaryl-4-hydroxyacetophenones (**3-4**) was effected under various conditions [15]. Thus, the 2-hydroxy-4-methoxyketones were converted fairly readily by condensation with diethyl carbonate in the presence of sodium *tert*-butanolate at room temperature into the derrusnin analogs (**3**). The conversion of the

*KIEN, Karakalpak Division, Academy of Sciences of the Republic of Uzbekistan, Nukus. †Taras Shevenko Kiev University, Kiev, Ukraine. Translated from Khimiya Prirodnykh Soedinenii, No. 2, pp. 226-230, March-April, 1994. Original article submitted August 10, 1993.

0009-3130/94/3002-0207$12.50

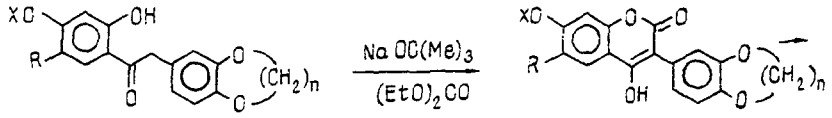
TABLE 1. Characteristics of Compounds (**3-5**)

Compound	Yield, %	mp, °C	Empirical formula	Solvent for crystallization
3a	68	171—172	$C_{18}H_{14}O_6$	EtOAc
3b	64	205—206	$C_{20}H_{18}O_6$	EtOH
3c	61	201—202	$C_{19}H_{16}O_6$	EtOH
4b	56	258—259	$C_{19}H_{16}O_6$	EtOH/H_2O
4c	54	252—253	$C_{18}H_{14}O_6$	EtOH/H_2O
4d	47	223—224	$C_{19}H_{16}O_6$	EtOH/H_2O
5a	86	165—166	$C_{20}H_{16}O_7$	EtOAc/ hexane
5b	93	189—190	$C_{22}H_{20}O_7$	EtOAc
5c	88	166—167	$C_{21}H_{18}O_7$	EtOAc

TABLE 2. IR and UV Spectra of the Derrusnin Analogs (**3-5**)

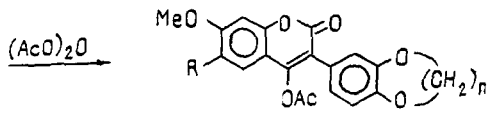
Compound	IR spectrum, ν, cm^{-1}				UV spectrum, λ_{max}, nm (log ε)
	νC=O	νOAc	νOH	skeletal vibrations	
3a	1685		3280	1615, 1585, 1510	205(4.64); 216(4.68); 256(4.17); 340(4.19);
3b	1690		3450	1615, 1585, 1552, 1500	205(4.58); 217(4.63); 256(4.11); 325(4.20)
3c	1685		3460	1610, 1555, 1500	204(4.61); 215(4.67); 258(4.14); 340(4.22)
4b	1690		3280	1625, 1565, 1500	204(4.60); 216(4.60); 257(4.08); 320(4.23)
4c	1680		3210 3340	1605, 1580, 1555, 1500	204(4.64); 257(4.16); 320(4.24)
4d	1685		3280	1620, 1595, 1560, 1500	201(4.55); 220(4.59); 258(4.09); 320(4.24)
5a	1710	1770		1610, 1580, 1565, 1500	210(4.72); 245(3.98); 290(3.83); 340(4.27)
5b	1705	1775		1610, 1575, 1500	211(4.70); 249(3.98); 290(3.79); 354(4.28)
5c	1705	1760		1605, 1565, 1500	203(4.74); 243(4.04); 282(3.88); 335(4.32)

2,4-dihydroxy derivatives (**2**) into the 4,7-dihydroxycoumarins (**4**) took place under the action of the same reagents on heating to 120-125°C. The action of acetic anhydride on compounds (**3**) led to the 4-acetoxy derivatives (**5**).



1 a-c, 2 b-d

3 a-c, 4 b-d



5 a-c

a: R=H, n=2; b: R=Et, n=2; c: R=H, n=3; d: R=Pr, n=1; 1,3: X=Me; 2,4: X=H

The 3-hetarylcoumarins obtained were colorless crystalline substances readily soluble in the majority of solvents and insoluble in water. The characteristics of compounds (**3-5**) are given in Table 1.

The structures of the coumarins (**3-5**) obtained were confirmed by their UV and IR (Table 2) and PMR (Table 3) spectra.

TABLE 3. Chemical Shifts in the PMR Spectra (δ, ppm, J, Hz) of the Derrusnin Analogs (3-5) (in DMSO-d_6)

Compound	Protons of the coumarin ring				
	OH-4 or OAc-4, s	H-5, d J=8 Hz	H-6, dd J=8 Hz J=2 Hz or R=6	OH-7 or OMe-7, s	H-8, d J=2 Hz
3a	11.03	7.89	6.93 m	3.88	6.93 m
3b	11.00	7.71 c	2.62 q; 1.17 t	3.90	6.97 s
3c*	6.75	7.78	6.89	3.89	7.05
	9.82	7.87	7.06	3.88	7.03
4b	10.56	7.73 c	2.65 q; 1.22 t	10.56	6.80 s
4c	10.63	7.86	6.85	10.63	6.77
4d	10.56	7.71 c	2.61 t; 1.63 m; 0.95 t	10.56	6.81 s
5a	2.18	7.37	6.86	3.86	6.86
5b	2.20	7.16 c	2.65 q; 1.19 t	3.89	6.82
5c	2.17	7.36	6.85	3.87	6.85

Compound	Protons of the hetaro residue			
	H-4, H-5 or H-6 d J=2 Hz	H-6, H-7 or H-8 dd J=8 Hz J=2 Hz	H-7, H-8 or H-9 d, J=8 Hz	$-O(CH_2)_nO$ c
3a	6.93 m	6.93 m	6.93 m	4.31
3b	6.87	6.83	6.89	4.28
3c*	6.90	6.84	7.07	4.24 t; 2.2 q
	6.88	6.82	6.82	4.21 t; 2.19 q
4b	6.91 m	6.91 m	6.91 m	4.28
4c	7.02 m	7.02 m	7.02 m	4.19 t; 214 q
4d	6.95	6.88	6.96	6.07
5a	6.89	6.97	6.89	4.26
5b	6.89	6.97	6.89	4.26
5c	7.0	7.06	7.00	4.23 t; 2.17 q; 4.21 t

*Spectrum taken in $CDCl_3$.

The IR spectra of coumarins (3, 4) showed absorption bands corresponding to the stretching vibrations of C=O groups in the 1685-1690 cm^{-1} region, and for compounds (5) the stretching vibrations of acetyl groups were observed at 1760-1775 cm^{-1} and $\nu_{C=O}$ bands at 1705-1710 cm^{-1}.

In each of the UV spectra of compounds (3,4) there were three short-wave absorption maxima in the 201-258 nm region and one long-wave maximum in the 320-340 nm region; the spectra of compounds (5) had the same form at 203-290 and 335-354 nm, respectively.

In the PMR spectra of the 4-hydroxycoumarins (3-4) (in DMSO) the protons of the OH-4 hydroxyls gave signals at 9.8-11.0 ppm. The closure of the coumarin rings caused downfield shifts of the H-6 and H-8 signals by 0.39-0.57 ppm in compounds (3-4), while the signals of the H-5 protons were observed at the same point in the spectrum as the signals of the corresponding H-6 protons in the initial ketones. The spin-spin coupling between the aromatic protons H-5, H-6, and H-8 remained almost the same as in the initial ketones (1) and (2). These protons formed spin systems with $J_{5,6}$ = 8 Hz and $J_{6,8}$ = 2 Hz. The signals of the OH-7 groups in compounds (4) were observed in the 10.5-10.6 ppm region. The spectra of the 7-methoxycoumarins (3) lacked the signals of the protons of phenolic hydroxyls, in place of which there were the singlets of methoxy groups at 3.9 ppm.

In the PMR spectra of the 4-acetoxycoumarins (5), in place of the signals of hydroxy groups the three-proton signal of acetyl groups appeared at 2.2 ppm.

Thus, the cyclization of α-hetaryl-2-hydroxyacetophenones under the action of diethyl carbonate in the presence of sodium *tert*-butanolate takes place readily and with good yields of the desired products — synthetic derrusnin analogs.

EXPERIMENTAL

3-Hetaryl-4-hydroxy-7-methoxycoumarins (3a-c). With stirring at room temperature in an inert gas atmosphere, 9.6 g (100 mmole) of sodium *tert*-butanolate was added to a mixture of 10 mmole of a ketone (**1a-c**) in 30 ml of diethyl carbonate. The reaction mixture was stirred at room temperature for another 3-6 h, and then the solvent was evaporated off. The dry residue was dissolved in cold water and the solution was acidified with dilute hydrochloric acid to pH 2-3. The precipitate that deposited was filtered off and crystallized from a suitable solvent.

3-Hetaryl-4,7-dihydroxycoumarins (4b-d). With stirring at room temperature in an inert gas atmosphere, 9.6 g (100 mmole) of sodium *tert*-butanolate was added to a mixture of 10 mmole of a ketone (**2b-d**) and 30 ml of diethyl carbonate. The reaction mixture was heated at 120-125°C with stirring for 20-120 min, after which the solvent was evaporated off. The dry residue was dissolved in cold water and the solution was acidified to pH 2-3. The precipitate that deposited was filtered off and crystallized from aqueous alcohol.

3-Hetaryl-4-acetoxy-7-methoxycoumarins (5a-c). A solution of 3 mmole of a coumarin (**3a-c**) in 18 ml of freshly distilled acetic anhydride was boiled for 10 min. The reaction mixture was left at room temperature for several hours and then in a refrigerator overnight. The precipiate that had deposited was filtered off and was carefully washed with cold alcohol. The compounds obtained were crystallized from suitable solvents.

REFERENCES

1. A. Aitmambetov and V. P. Khilya, Khim. Prir. Soedin. [in this issue].
2. I. I. Grandberg, L. K. Denisov, and O. A. Popova, Khim. Prir. Soedin., No. 2, 147 (1987).
3. A. J. East, W. D. Hollis, and R. E. Wheeler, J. Chem. Soc., Chem. Commun., 365 (1969).
4. R. D. H. Murray, Nat. Prod. Rept., **6**, 591 (1989).
5. A. B. Ray and S. K. Chattopadhyay, Tetrahedron Lett., **21**, 4477 (1980).
6. A. B. Ray, S. K. Chattopdhyay, S. Kumar, C. Konno, V. Kiso, and H. Hikino, Tetrahedron, **41**, 209 (1985).
7. S. Kumar, A. B. Ray, C. Konno, Y. Oshima, and H. Hikino, Phytochemistry, **27**, 636 (1988).
8. T. Shamsuddin, W. Rahman, S. A. Khan, K. M. Shamsuddin, and J. R. Kintzinger, Phytochemistry, **27**, 1908 (1988).
9. L. J. Lin and G. A. Cordell, J. Chem. Res. (S), No. 12, 396 (1988).
10. H. Tanaka, I. Kato, K. Ita, Chem. Pharm Bull., **33**, 3218 (1985).
11. G. Guillaumet, M. Hretani, G. Coudert, and S. Averbeck, Eur. J. Med. Chem., **25**, No. 1, 45 (1990).
12. A. Aitmambetov and V. P. Khilya, Khim. Prir. Soedin., 669 (1993).
13. A. Aitmambetov, L. P. Grishko, and V. P. Khilya, Khim. Prir. Soedin., 808 (1993).
14 A. Aitmambetov, L. P. Grishko, and V. P. Khilya, Khim. Prir. Soedin., 814 (1993).
15. B. Sreenivasulu, V. Sundaramurthy, and N. V. S. Rao, Proc. Indian Acad. Sci., Sec. A, **80**, No. 46, 273 (1974).