Synthesis of new chalcone analogues and derivatives

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The synthesis of new derivatives of 2′-hydroxychalcone, such as esters, sulfonates, and thiocarbamates, prepared for evaluation as antiparasitic agents as well as new heterocyclic chalcone analogues prepared for the same purpose, is described.

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In a search for a new gastrointestinal anthelmintic with a broad spectrum of biological activity, a number of chalcones and related compounds were prepared and evaluated as antiparasitic agents (1). In this study a weak anthelmintic activity of chalcone was discovered and the activity has been increased by the addition of a hydroxyl group in position-2′. Derivatives of this phenol have also exhibited increased anthelmintic activity. The new aryl esters, sulfonates, and the thiocarbamate of 2′-hydroxychalcone which were prepared and submitted for testing are herein described.

To establish structure–activity relationship in this series, chemical manipulations to evaluate the importance of the two phenyl groups in the chalcone molecule were made. New chalcone analogues in which one of the phenyl rings is replaced by a heterocyclic ring were prepared by the Claisen–Schmidt condensation of an appropriate aldehyde with a convenient methylketone, using methanol or ethanol as solvent and sodium hydroxide as base.

Experimental

General Procedure (Claisen–Schmidt Condensation)

Two ml of 40% sodium hydroxide was added to a solution of the appropriate aldehyde (0.05 *M*) and the methylketone (0.05 *M*) in methanol. The solution became yellow and generally a solid appeared on standing for a few hours. It was removed by filtration and was crystallized from an appropriate solvent as described in Table I. If no solid formed, the solvent was evaporated under vacuum and the substance was extracted with dichloromethane. The solvent was washed with water and then dried and evaporated. The residue was crystallized from an appropriate solvent (see Table I).

Esters from 2′-Hydroxychalcone

Method a

The technique used has been described by Spasov (2). A benzene solution (300 ml) of 2′-hydroxychalcone (0.03 *M*) and of an appropriate acid chloride (0.04 *M*) was kept under reflux for 4 days in the presence of magnesium turnings (11 g). The mixture was cooled and the magnesium was removed and washed with ether. The solvents were washed to neutrality with 5% NaOH and water. Evaporation yielded a heavy oil that could not be distilled without decomposition. This oil was either crystallized as described in Table II or it was purified by passing it through silicic acid as it was for the cinnamate which did not crystallize.

Method b: the Preparation of Sulfonates

To a solution of 2′-hydroxychalcone (0.01 *M*) in 25 ml of pyridine was added a tenfold excess of a sulfonyl chloride. After 18 h, water was added. The substance was placed in benzene and washed. After evaporation it was crystallized from ether and from methylcyclohexane to give light-yellow solids described in Table II.

2′-Hydroxy-β-N-morpholinoacrylophenone

A mixture of 2′-hydroxy-β-formylacetophenone (3) (0.02 *M*) and morpholine (0.02 *M*) was heated on a steam bath for 1 h. The crude solid crystallized from ethanol to give yellow crystals (85% yield) melting at 107–108 °C; ultraviolet (u.v.), λ_{max} at 256 mμ.

Anal. Calcd. for $C_{13}H_{15}NO_3$: C, 66.93; H, 6.48; N, 6.01. Found: C, 62.17; H, 6.64; N, 5.94.

2′-Hydroxy-β-N(N′-phenyl)piperazinoacrylophenone

A mixture of 2′-hydroxy-β-formylacetophenone (3) (0.02 *M*) and *N*-phenylpiperazine was heated on a steam bath for 1 h. The crude solid obtained was crystallized from ethanol to give yellow crystals (75% yield) melting at 114–115 °C; u.v. λ_{max}, at 230 and 248 mμ.

Anal. Calcd. for $C_{19}H_{20}N_2O_2$: C, 74.00; H, 6.54; N, 9.09. Found: C, 74.20; H, 6.34; N, 8.76.

Di(2′-hydroxychalcone)thiocarbonate

The triethylamine salt of 2′-hydroxychalcone (0.03 *M*) was prepared by adding triethylamine (0.03 *M*) to an equivalent of 2′-hydroxychalcone in benzene (60 ml). This solution was added dropwise with stirring to a cooled solution of thiophosgene (0.03 *M*) in benzene (60 ml). After 2 h, another portion of thiophosgene (0.01 *M*) with an equivalent of triethylamine was added. The reaction mixture was allowed to come to room temperature and it was stirred for a further 2 h. The solvent was removed to give a brown oil which crystallized on addition of ether. Recrystallization from ethanol yielded a pale-yellow solid (65% yield) melting at 131–132 °C; u.v. λ_{max}, at 227 and 306 mμ.

Anal. Calcd. for $C_{31}H_{22}O_4S$: C, 75.91; H, 4.52; S, 6.52. Found: C, 75.54; H, 4.58; S, 6.55.

TABLE I

Experimental data for new chalcone analogues and derivatives

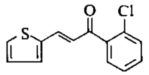
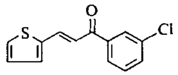
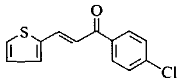
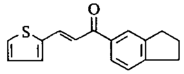
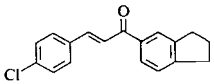
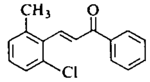
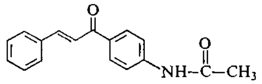
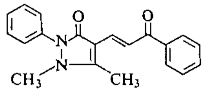
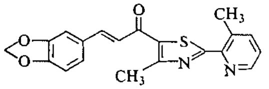
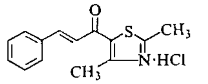
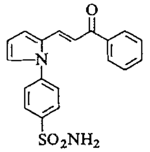
Compound	Melting point (°C)	Yield (%)	Solvent of crystalization	Molecular formula	Analyses										Infrared† C=O (cm^{-1})
					Calculated					Found					
					C	H	Cl	N	S	C	H	Cl	N	S	
	31–32	40	Methylene chloride* and hexane	$C_{13}H_9ClOS$	62.90	3.66	14.25		12.87	62.84	3.70	14.18		12.95	1655
	95–96	85	Methanol	$C_{13}H_9ClOS$	62.90	3.66	14.25		12.87	62.98	3.73	14.33		12.96	1658
	121–122	90	Methanol	$C_{13}H_9ClOS$	62.90	3.66	14.25		12.87	63.11	3.93	14.62		12.86	1655
	89–90	50	Methanol* and water	$C_{16}H_{14}OS$	75.57	5.55			12.58	75.32	5.67			12.83	1655
	190–191	55	Ethyl acetate	$C_{18}H_{15}ClO$	76.45	5.35	12.54			76.54	5.26	12.55			1662
	56–57	65	Methanol	$C_{16}H_{13}ClO$	74.87	5.32	13.81			74.63	5.10	13.79			1662

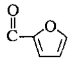
TABLE I (*Concluded*)

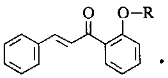
Compound	Melting point (°C)	Yield (%)	Solvent of crystallization	Molecular formula	Analyses										Infrared* C═O (cm^{-1})
					Calculated					Found					
					C	H	Cl	N	S	C	H	Cl	N	S	
	163–164	65	Ethanol	$C_{17}H_{15}NO_2$	76.96	5.70		5.28		76.70	5.71		5.28		1655
	194–196	50	Isopropyl alcoho	$C_{20}H_{18}N_2O_2$	75.45	5.70		8.80		75.77	5.88		8.73		1663
	208–209	75	Ethyl acetate	$C_{20}H_{16}N_2O_3S$	65.93	4.43		7.69	8.78	66.09	4.53		7.60	9.16	1648
	127–130	25	Methanol†	$C_{14}H_{13}NOS{\cdot}HCl$			12.67	5.01	11.45			12.89	4.92	11.92	1660
	165–167	60	Toluene	$C_{19}H_{16}N_2O_3S$	64.77	4.58		7.95	9.08	65.01	4.67		7.96	9.13	1647

*In chloroform solution.
†These substances were extracted with dichloromethane from the residue after evaporation of the methanol.

TABLE II

Esters* of 2′hydroxychalcone

R	Method	Melting point (°C)	Solvent of crystallization	Yield (%)	Molecular formula	Analyses: Calculated C	Calculated H	Calculated S	Found C	Found H	Found S	Ultraviolet† λ_{max} (mμ)	Infrared‡ (cm⁻¹) ketone	Infrared‡ (cm⁻¹) ester
$\overset{O}{\overset{\|}{C}}$—CH=CH$_2$	*a*	Oil		60	$C_{18}H_{14}O_3$	77.68	5.07		77.45	4.83		223, 304	1640	1740
$\overset{O}{\overset{\|}{C}}$—C$_6H_5$	*a*	90–91	Benzene and 25% hexane	70	$C_{22}H_{16}O_3$	80.47	4.91		80.23	4.86			1645	1740
$\overset{O}{\overset{\|}{C}}$—CH$_2$—C$_6H_5$	*a*	118	Benzene	70	$C_{23}H_{18}O_3$	80.35	5.59		80.68	5.30			1645	1757
$\overset{O}{\overset{\|}{C}}$—CH=CH—C$_6H_5$	*a*	71–72	Propanol	65	$C_{24}H_{18}O_3$	81.34	5.12		81.16	5.15		223, 289	1640	1728
	*a*	92	Ether and 40% hexane	70	$C_{20}H_{14}O_4$	75.46	4.43		75.78	4.65			1645	1740
SO$_2$CH$_3$	*b*	98–99	Methylcyclohexane	50	$C_{16}H_{14}O_4S$	63.57	4.67	10.58	63.69	4.85	10.58	228, 305	1650	
SO$_2$C$_6$H$_5$	*b*	88	Methylcyclohexane	30	$C_{21}H_{16}O_4S$	69.22	4.43	8.78	69.31	4.65	8.86	221, 308	1646	

*Compounds of structure 

†In ethanol solutions.
‡In chloroform solutions.

2,2′-Dicinnamoxychalcone

Triethylamine (0.01 *M*) was added to 2,2′-dihydroxychalcone (0.005 *M*) in hot toluene (20 ml). Cinnamoyl chloride (0.01 *M*) in toluene was added slowly with constant stirring and the mixture was heated under reflux for 90 min. Similar addition is repeated. The mixture was cooled and then it was washed with water and extracted with toluene. After removal of the solvent, the oil was crystallized from propanol to give a yellow solid (65% yield) melting at 126–127 °C; u.v. λ_{max} at 282 mμ.

Anal. Calcd. for $C_{33}H_{24}O_5$: C, 79.18; H, 4.83. Found: C, 79.34; H, 4.96.

2-(N-Phenylcarbamyl)oxy-2′-hydroxychalcone

Phenyl isocyanate (0.01 *M*) was added to 2,2′-dihydroxychalcone (0.005 *M*) in hot toluene (30 ml). Five drops of pyridine were added and the mixture was heated under reflux for 1 h. The solvent was evaporated to give a yellow solid. Recrystallization from acetone by the addition of hexane gave a yellow solid (35% yield) melting at 167–169 °C; u.v. λ_{max} at 237 and 313 mμ.

Anal. Calcd. for $C_{22}H_{17}NO_4$: C, 73.53; H, 4.77; N, 3.90. Found: C, 73.19; H, 4.78; N, 3.82.

1. R. Laliberté, D. Campbell, and F. Bruderlein. Can. J. Pharm. Sci. **2**, 37 (1967).
2. A. Spasov. Ber. **75B**, 779 (1942); Chem. Abstr. **36**, 7010.
3. A. Schönberg and A. Sina. J. Am. Chem. Soc. **72**, 3397 (1950).