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Synthesis of new chalcone analogues and derivatives

Réal L'Aliberté, Jane Manson, Hilda Warwick, and George Medawar

Department of Chemistry, Ayerst Research Laboratories, Ayerst, McKenna, and Harrison Limited, Montréal, Québec

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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-\beta-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 m μ .

Anal. Calcd. for C₁₃H₁₅NO₃: 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 C₁₉H₂₀N₂O₂: 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.

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 TABLE I

 Experimental data for new chalcone analogues and derivatives

| | | | | | | | | | Ar | alyses | | | | | | |
|---------------------------------------|------------|-------|-----------------------------------|-------------------------------------|-------|------|-----------|----|-------|--------|------|-------|---|-------|---------------------|-------|
| | Melting | Yield | Solvent of | Molecular | | | Calculate | ed | | | | Found | | | Infrared† C=O | |
| Compound | point (°C) | (%) | crystalization | formula | С | н | Cl | N | S | С | н | Ci | N | S | (cm ⁻¹) | |
| S CI | 31-32 | 40 | Methylene chloride* and hexane | C13H9ClOS | 62.90 | 3.66 | 14.25 | | 12.87 | 62.84 | 3.70 | 14.18 | | 12.95 | 1655 | |
| CI CI | 95-96 | 85 | Methanol | C13H9ClOS | 62.90 | 3.66 | 14.25 | | 12.87 | 62.98 | 3.73 | 14.33 | | 12.96 | 1658 | NOTES |
| s C | 121-122 | 90 | Methanol | C13H9CIOS | 62.90 | 3.66 | 14.25 | | 12.87 | 63.11 | 3.93 | 14.62 | | 12.86 | 1655 | S |
| S S S S S S S S S S S S S S S S S S S | 89-90 | 50 | Methanol* and water | $C_{16}H_{14}OS$ | 75.57 | 5.55 | | | 12.58 | 75.32 | 5.67 | | | 12.83 | 1655 | |
| | 190191 | 55 | Ethyl acetate | C ₁₈ H ₁₅ ClO | 76.45 | 5,35 | 12.54 | | | 76.54 | 5.26 | 12.55 | | | 1662 | |
| CH ₃ O | 56–57 | 65 | Methanol | C ₁₆ H ₁₃ ClO | 74.87 | 5.32 | 13.81 | | | 74.63 | 5.10 | 13.79 | | | 1662 | |

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| | | | | | | | | | An | alyses | | | | | |
|--|------------|-------|------------------|---|-------|------|-----------|------|-------|--------|------|-------|---------------|--------------|---------------------|
| | Melting | Yield | Solvent of | Molecular | | C | Calculate | ed | | | | Found | | | Infrared* C=O |
| Compound | point (°C) | (%) | crystallization | formula | c | н | Cl | N | S | с | Н | CI | N | S | (cm ⁻¹) |
| O NH-C-CH ₃ | 163–164 | 65 | Ethanol | C17H15NO2 | 76.96 | 5.70 | | 5.28 | | 76.70 | 5.71 | | 5.28 | | 1655 |
| CH ₃ ^O O CH ₃ ^O CH ₃ | 194–196 | 50 | Isopropyl alcoho | C20H18N2O2 | 75.45 | 5.70 | | 8.80 | | 75.77 | 5.88 | | 8.73 | | 1663 |
| | 208-209 | 75 | Ethyl acetate | C ₂₀ H ₁₆ N ₂ O ₃ S | 65.93 | 4.43 | | 7.69 | 8.78 | 66.09 | 4.53 | | 7.60 | 9 .16 | 1648 |
| CH ₃ CH ₃ CH ₃ CH ₃ CH ₃ CH ₃ | 127-130 | 25 | Methanol† | C14H13NOS·HCl | | | 12.67 | 5.01 | 11.45 | | | 12.89 | 4. 9 2 | 11.92 | 1660 |
| | 165-167 | 60 | Toluene | C19H16N2O3S | 64.77 | 4.58 | | 7.95 | 9.08 | 65.01 | 4.67 | | 7. 9 6 | 9.13 | 1647 |
| SO ₂ NH ₂ | | | | | | | | | | | | | | | |

TABLE I (Concluded)

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

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| TABLE II | Esters* of 2'hydroxychalcone |
|----------|------------------------------|
|----------|------------------------------|

| R Method Point (°C) Solvent of crystallization Yield (?2) Molecular formula C H Found Ultraviolet (mpl) Molecular ketone CH ₁ a Oil C H S C H S Oil λ_{max}^{nas} CH ₁ a Oil C rst S C H S C H S Oil λ_{max}^{nas} Molecular λ_{max}^{nas} λ_{max}^{nas} Molecular λ_{max}^{nas} Molecular λ_{max}^{nas} $\lambda_{max}^{nas}^{nas}$ λ_{ma | R Method Mething Solvent of crystallization Yield Moleculated Found CH ₂ a Oil Cystallization (%) formula C H S C H S CH ₂ a Oil Solvent of (%) fried Moleculated C H S C H S CH ₂ a Oil Solvent of (%) C H S | | | | | | | | Analyses | yses | | | T. fan | + 100 |
|--|---|----------------------------------|--------|------------|-------------------------------|---------------|--|------------|----------|-----------|-------|------------------|------------------|-------|
| R Method method control right Montand C H S Method m | R Method motion conditation read Motion C H S C H S CH ₂ a Oil C C H S C H S CH ₂ a Oil C T S < | | | | ن - ۱۰ ن | EL. | Malandar | Calculate | p | Fou | pu | Ultraviolet | (cm ⁻ | †n: - |
| $ \begin{array}{c cccc} CH_{2} & a & Oil \\ cH_{1} & a & Oil \\ cH_{2} & a & Oil \\ cH_{2} & a & 0^{0}-91 & Benzene and \\ 25\% hexane \\ c_{6}H_{5} & a & 118 & Benzene and \\ c_{5}H_{16}O_{5} & 80.47 & 4.91 & 80.23 & 4.86 \\ c_{23}H_{16}O_{5} & 80.47 & 4.91 & 80.23 & 4.86 \\ c_{24}H_{16}O_{5} & 80.35 & 5.59 & 80.68 & 5.30 \\ cH_{-}C_{6}H_{5} & a & 71-72 & Propanol & 65 & C_{24}H_{16}O_{5} & 81.34 & 5.12 \\ cH_{-}C_{6}H_{5} & a & 71-72 & Propanol & 65 & C_{24}H_{16}O_{5} & 81.34 & 5.12 \\ cH_{-}C_{6}H_{5} & a & 71-72 & Propanol & 65 & C_{24}H_{16}O_{5} & 81.34 & 5.12 & 81.16 & 5.15 \\ cH_{-}C_{6}H_{5} & a & 71-72 & Propanol & 65 & C_{24}H_{16}O_{5} & 81.34 & 5.12 & 81.16 & 5.15 \\ cH_{-}C_{6}H_{5} & a & 71-72 & Propanol & 65 & C_{24}H_{16}O_{5} & 81.34 & 5.12 & 81.16 & 5.15 & 223,289 & 1640 \\ cH_{-}C_{6}H_{5} & a & 71-72 & Propanol & 65 & C_{16}H_{14}O_{4} & 75.46 & 4.43 & 71.76 & 4.65 & 8.66 & 4.85 & 10.58 & 228,305 & 1650 \\ cH_{-} & cH_{-} & cH_{-} & cH_{-}CO_{5} & cH_{-}CO_$ | CH1 a Oil Oil $C_{18}H_{14}O_{2}$ 77.68 5.07 77.45 4.83 a 90-91 Benzene and 25% hexane 70 $C_{22}H_{16}O_{3}$ 80.47 4.91 80.23 4.83 4.83 C ₆ H3 a 90-91 Benzene and 25% hexane 70 $C_{23}H_{16}O_{3}$ 80.47 4.91 80.23 4.86 5.30 C ₆ H3 a 71-72 Propanol 70 $C_{23}H_{16}O_{3}$ 80.47 4.91 80.68 5.30 C ₆ H3 a 71-72 Propanol 50 $C_{24}H_{18}O_{3}$ 81.34 5.12 81.16 5.12 -C 6 70 $C_{20}H_{14}O_{4}$ 70 5.14 6.73 4.67 0.58 6.50 4.65 10.58 6 9 9 9 9 $0.51H_{16}O_{4}$ 6.73 4.67 10.58 6.56 10.58 10.58 10.58 6 9 9 2 $10+16O_{16}$ $10-16_{16}$ $10-16_{16}$ 1 | R | Method | point (°C) | solvent of crystallization | r ield (%) | formula | | s | | | xem _V | ketone | ester |
| | s 90-91 Benzene and 25% hexane 70 $C_{22}H_{16}O_{3}$ 80.47 4.91 80.23 4.86 -C_6H_5 a 118 Benzene 70 $C_{23}H_{18}O_{3}$ 80.47 4.91 80.23 4.86 -C_6H_5 a 118 Benzene 70 $C_{23}H_{18}O_{3}$ 80.35 5.59 80.68 5.30 -CHC_6H_5 a 71-72 Propanol 65 $C_{24}H_{18}O_{3}$ 81.34 5.12 81.16 5.15 a 92 Ether and 40% hexane 70 $C_{20}H_{14}O_{4}S$ 81.34 5.12 81.16 5.15 b 98–99 Methyleyclohexane 50 $C_{16}H_{14}O_{4}S$ 63.57 4.67 10.58 63.69 4.65 c b 98 Methyleyclohexane 50 $C_{16}H_{14}O_{4}S$ 69.21 4.65 10.58 69.31 4.65 8.86 | =CH2 | a | Oil | | 60 | C ₁₈ H ₁₄ O ₃ | 77.68 5.07 | | 77.45 4.8 | 5 | 223, 304 | | 1740 |
| $-C_6H_5 \qquad a \qquad 118 \qquad Benzene \qquad 70 \qquad C_{23}H_{18}O_3 \qquad 80.35 5.59 \qquad 80.68 5.30 \qquad 1648 \qquad 1645 \qquad 1646 \qquad -CH-C_6H_5 \qquad a \qquad 71-72 \qquad Propanol \qquad 65 \qquad C_{24}H_{18}O_3 \qquad 81.34 5.12 \qquad 81.16 5.15 \qquad 223,289 \qquad 1640 \qquad 1640 \qquad -26 \qquad -27 \qquad -26 \qquad -26$ | $ \begin{array}{ ccc} -C_{6}H_{5} & a & 118 & Benzene & 70 & C_{13}H_{18}O_{3} & 80.35 & 5.59 & 80.68 & 5.30 \\ =CHC_{6}H_{4} & a & 71-72 & Propanol & 65 & C_{24}H_{18}O_{3} & 81.34 & 5.12 & 81.16 & 5.15 \\ & & & & & & & & & & & & & & & & & & $ | Is | σ | 90-91 | Benzene and 25% hexane | 70 | C22H16O3 | 80.47 4.91 | | | 36 | | 1645 | 1740 |
| $ \begin{array}{ccccc} CH-C_6H_5 & a & 71-72 \\ & & 71-72 \\ & & Propanol \\ & & 92 \\ & & 40\% hexane \\ b & 98-99 \\ & & Methylevelohexane \\ & & 50 \\ & & C_{16}H_{14}O_4 \\ & & 75.46 \\ & 4.43 \\ & & 75.78 \\ & 4.65 \\ & & 4.65 \\ & & 4.85 \\ & & 10.58 \\ & & 228,305 \\ & & 1650 \\ & & 1650 \\ & & 1646 \\ & & & & & & & & & & & & \\ \end{array} $ | $ \begin{array}{c c c c c c c c c c c c c c c c c c c $ | CH₂—C₀H₅ | a | 118 | Benzene | 70 | $C_{23}H_{18}O_{3}$ | 80.35 5.59 | | | 0 | | 1645 | 1757 |
| a 92 Ether and 40% hexane 70 $C_{20}H_{14}O_{4}$ 75.46 4.43 75.78 4.65 b 98-99 Methyleyclohexane 50 $C_{16}H_{14}O_{4}S$ 63.57 4.67 10.58 63.10.58 228,305 1650 b 88 Mathyleyclohexane 50 $C_{1H_{4}O_{4}S}$ 63.57 4.67 10.58 63.69 4.85 10.58 228,305 1650 b 88 Mathyleyclohexane 30 $C_{1H_{4}O_{5}S}$ 60.31 465 8.66 311.408 1646 | a 92 Ether and 40% hexane 70 $C_{20}H_{14}O_4$ 75.46 4.43 75.78 4.65 b 98–99 Methylecyclohexane 50 $C_{16}H_{14}O_4S$ 63.57 4.67 10.58 63.69 4.85 10.58 s b 88 Methylecyclohexane 30 $C_{21}H_{16}O_4S$ 69.22 4.43 8.76 69.31 4.65 8.86 | =CHC ₆ H ₅ | a | 71–72 | Propanol | 65 | $C_{24}H_{18}O_{3}$ | 81.34 5.12 | | 81.16 5.1 | S | 223, 289 | 1640 | 1728 |
| b 98–99 Methyleyclohexane 50 $C_{16}H_{14}O_{4}S$ 63.57 4.67 10.58 63.69 4.85 10.58 228,305 E 28, 305 E 28, 305 E 201 201 E 201 E 201 201 E 201 201 E 201 | b 98-99 Methylcyclohexane 50 $C_{16}H_{14}O_4S$ 63.57 4.67 10.58 63.69 4.85 10.58 b 88 Methylcyclohexane 30 $C_{21}H_{16}O_4S$ 69.22 4.43 8.78 69.31 4.65 8.86 | | a | 92 | Ether and 40 % hexane | 70 | C ₂₀ H ₁₄ O ₄ | 75.46 4.43 | | 75.78 4.6 | 22 | | 1645 | 1740 |
| ь ве Майнонононоволо 30 С.,Н.,О.S. 60.22.4.3.8.78.60.31.4.65.8.86.221.308 | b 88 Methylcyclohexane 30 C ₂₁ H ₁₆ O ₄ S 69.22 4.43 8.78 69.31 4.65 8.86 | 5 | q | 66-86 | Methylcyclohexane | 50 | C ₁₆ H ₁₄ O ₄ S | 4.67 | 10.58 | 63.69 4.8 | 10.58 | 228, 305 | 1650 | |
| | Ļ | H _s | q | 88 | Methylcyclohexane | 30 | $C_{21}H_{16}O_4S$ | 69.22 4.43 | 8.78 | 69.31 4.6 | | | 1646 | |

2,2'-Dicinnamoxychalcone

1956

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 C₃₃H₂₄O₅: C, 79.18; H, 4.83. Found:

C, 79.34; H, 4.96,

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

Phenyl isocyanate (0.01 \dot{M}) was added to 2,2'-dihy-droxychalcone (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 C₂₂H₁₇NO₄: C, 73.53; H, 4.77; N, 3.90. Found: C, 73.19; H, 4.78; N, 3.82.

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