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Knoevenagel condensation of the β -ketosulfinyl intermediate II with butyl glyoxylate afforded the butyl 2-hydroxy-4-(2-hydroxyphenyl)-3-methylsulfinyl-4-oxobutyrate (III). Compounds III are versatile intermediates for the synthesis of either 2-chromonecarboxylates (V) or 2-carboxymethylene-3-coumaranone esters (VII).

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The discovery of a marked antiallergenic activity of disodium chromoglycate and its relatives (1) aroused an increasing interest in the chemistry of 2-chromonecarboxylic acids and prompted us to investigate new convenient synthetic routes to such substrates. β -Ketosulfoxides II appeared to be attractive intermediates, as they can be prepared from the cheap and easily available methyl salicylates I according to von Strandtmann, *et al.* (2).

Knoevenagel condensation of compounds IIa and IIb with glyoxylic acid *n*-butyl ester in chloroform at room temperature and in the presence of a catalytic amount of sodium acetate gave the ketols IIIa and IIIb in good yields. Both compounds were obtained as a mixture of two diastereoisomers (1:1) which can be detected by pmr and tlc analysis. Their separation was not accomplished owing to the low stability of such compounds towards the common chromatographic media. Only one pure diastereoisomer of each couple was isolated by crystallization from dry benzene.

Compounds III are versatile intermediates for the synthesis of either 2-chromonecarboxylates V or 2-carboxymethylene-3-coumaranone esters VII, into which they can be converted respectively by acid- or base-promoted cyclization. When a benzene solution of IIIa and IIIb was heated with an equimolecular amount of boron trifluoride etherate, the expected chromones Va or Vb were obtained in high yields; they can be in turn easily hydrolyzed in acidic medium into the carboxylic acids VIa and VIc.

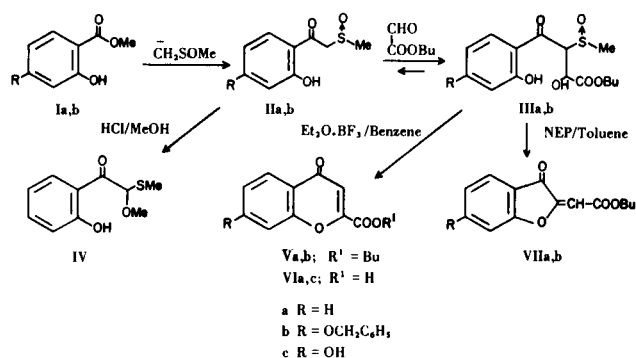
By treatment of IIIa with methanolic hydrogen chloride, monothioetheral IV was obtained originating by a *retro*-aldol reaction followed by an acid-promoted Pummerer rearrangement on the β -ketosulfinyl compound IIa so far produced. As a matter of fact, compound IV is also obtained from IIa under the same reaction conditions.

Alternatively, basic promoted cyclization of the intermediates IIIa and IIIb occurred in toluene at 60° containing a trace amount of *N*-ethylpiperidine (NEP) to afford coumaranones VIIa and VIIb.

The five-membered ring closure can be rationalized by assuming that in basic medium a nucleophilic intramolecular displacement of the sulfinyl group by the phenate ion can take place. Spontaneous loss of water from the resulting hydroxy intermediate provides the stable final compounds VII.

Both starting from one pure diastereoisomer of IIIa and IIIb or from their mixture, spectroscopic and chromatographic analysis revealed the presence of only one diastereoisomer for compounds VIIa and VIIb, the configuration of which was not ascertained. This finding could be explained both in terms of a sufficiently large energy difference between the transition states leading to the two diastereoisomeric hydroxy intermediates, and taking into account the easy enolization of the electrophilic center.

Compounds VIIa and VIIb, which are isomers of the corresponding chromones, were characterized by their ir, uv, pmr and ms spectra. In particular, the higher ir carbonyl stretching vibration at 1715 cm^{-1} (chromones, 1650 cm^{-1}) may be ascribed to ring strain of the five-membered ring (3). In addition, this value is only 5 cm^{-1} lower than that of the unsubstituted 3-coumaranone (4), indicating the presence of an exocyclic conjugate double bond. This system is also revealed by the pmr chemical shift of the vinylic proton which resonates at 6.17 ppm (VIIa) and 6.10 ppm (VIIb), that is about 1 ppm at higher field than the corresponding 2-chromonecarboxylic derivatives.



EXPERIMENTAL

Melting points were determined with a Büchi capillary apparatus and are uncorrected. Ir spectra were taken with a Perkin-Elmer 157 spectrophotometer. Pmr spectra were determined with a Perkin-Elmer R 12B spectrometer in deuteriochloroform (unless otherwise specified) using tetramethylsilane (TMS) as internal standard. Data are reported in δ ppm, from TMS. Uv spectra were determined with a Beckmann DB-GT spectrophotometer equipped with a W + W 1100 recorder. A Varian CH7 mass spectrometer

was used at the following conditions: ionization beam 20 eV and 60 μ A, ion source temperature 150°, accelerating voltage 3.0 KV. Tlc were run on plates of silica gel F₂₅₄ pre-coated, layer thickness 0.25 mm (Merck). Gas chromatographic analysis were realized with a Hewlett-Packard 5750 gas chromatograph equipped with a flame ionization detector (fid) and a glass column (2 m x 2 mm i.d.) coated with 3% OV-17 on Chromosorb W 80-100 mesh. The carrier gas (nitrogen) flow rate was 25 ml./minute.

Methyl 4-Benzoyloxy-2-hydroxybenzoate (Ib).

A mixture of methyl 2,4-dihydroxybenzoate (10 g., 60 mmoles), benzyl bromide (11 g., 65 mmoles), potassium carbonate (8.2 g., 60 mmoles) and acetone (200 ml.) was refluxed for 6 hours. After cooling, the inorganic precipitate was filtered off and the acetone removed by evaporation at reduced pressure. The residue was crystallized from benzene/hexane to give Ib (15.1 g., 97%), m.p. 100-101°; ir (cm⁻¹, oil mull): 3100 broad (ν OH phenol), 1670 (ν C=O ester, chelated).

Anal. Calcd. for C₁₅H₁₄O₄: C, 69.76; H, 5.46. Found: C, 69.98; H, 5.53.

2'-Hydroxy-2-methylsulfinylacetophenone (IIa).

This compound was prepared from methyl salicylate according to the described procedure, yield 80%, m.p. 152-153° (ethanol) (Lit. (2a,b) 151-153°).

4'-Benzoyloxy-2'-hydroxy-2-methylsulfinylacetophenone (IIb).

This compound was prepared in the same way, from methyl 4-benzoyloxy-2-hydroxybenzoate (Ib), yield 61%, m.p. 144-145° (ethanol); ir (cm⁻¹, oil mull): 3200 broad (ν OH phenol), 1635 (ν C=O ketone, chelated), 1020 (ν S-O).

Anal. Calcd. for C₁₆H₁₆O₄S: C, 63.14; H, 5.30; S, 10.53. Found: C, 63.23; H, 5.38; S, 10.42.

Butyl 2-Hydroxy-4-(2-hydroxyphenyl)-3-methylsulfinyl-4-oxobutyrates (IIIa).

A solution of IIa (5 g., 25 mmoles) in chloroform (100 ml.) was magnetically stirred at room temperature with butyl glyoxylate (5) (6.6 g., 50 mmoles) in the presence of a catalytic amount of anhydrous sodium acetate for 2 hours.

The solvent was removed by distillation *in vacuo* and the residue was taken up with isopropyl ether and filtered to give IIIa (6 g., 73%), m.p. 104-107°; tlc (ethyl ether/isopropyl ether 9:1, multiple development (6), number of runs: 6) showed that IIIa was a mixture of diastereoisomers which possess ⁶R_f = 0.38 and ⁶R_f = 0.44; ir (cm⁻¹, oil mull): 3200 (ν OH), 1745 and 1725 (ν C=O ester), 1630 (ν C=O ketone, chelated), 1025 (ν S-O).

Anal. Calcd. for C₁₅H₂₀O₆S: C, 54.86; H, 6.14; S, 9.76. Found: C, 54.70; H, 6.15; S, 9.92.

The diastereoisomer with ⁶R_f = 0.38 was isolated by crystallization from dry benzene, m.p. = 115-116°; pmr (perdeuterioacetone/DMSO-d₆ 4:1): 8.2 \div 7.45 complex absorption (2H: Ar-H), 7.2 \div 6.95 complex absorption (2H: Ar-H), 5.46 d (³J = 10 Hz; 1H: CO-CH-SO), 4.98 br d (³J = 10 Hz; 1H: HO-CH-CO), 4.02 center, complex absorption (2H: COOCH₂), 2.80 s (3H: SO-CH₃), 1.7 \div 1.0 complex absorption (4H: -CH₂-CH₂-CH₃), 1.0 \div 0.7 complex absorption (3H: CH₂-CH₃).

The characteristic chemical shifts of the diastereoisomer with ⁶R_f = 0.44 were determined from the pmr spectrum (perdeuterioacetone/DMSO-d₆ 4:1) of the mixture and are: 5.60 d (³J = 10 Hz; 1H: CO-CH-SO), 4.90 br d (³J = 10 Hz; 1H: HO-CH-CO), 4.05 center, complex absorption (2H: COOCH₂) and 2.78 s (3H: SO-CH₃).

Butyl 4-(4-Benzoyloxy-2-hydroxyphenyl)-2-hydroxy-3-methylsulfinyl-4-oxobutyrates (IIIb).

The compound was obtained in 67% yield from IIb using the procedure described for IIIa, m.p. = 104-114°; tlc (ethyl ether/isopropyl ether 1:1, multiple development (6), number of runs: 6) showed that IIIb was a mixture of diastereoisomers which possess ⁶R_f = 0.21 and ⁶R_f = 0.27; ir (cm⁻¹, oil mull): 3340 (ν OH, alcohol), 1745 (ν C=O ester), 1630 (ν C=O ketone, chelated), 1055 (ν S-O).

The diastereoisomer with ⁶R_f = 0.21 was isolated (7) by crystallization from dry benzene, m.p. = 127-129°.

Anal. Calcd. for C₂₂H₂₆O₇S: C, 60.81; H, 6.03; S, 7.38. Found: C, 60.67; H, 5.95; S, 7.29.

Butyl 2-Chromonecarboxylate (Va).

A mixture of IIIa (0.5 g., 1.5 mmoles), dry benzene (50 ml.) and boron trifluoride etherate (0.2 g., 1.5 mmoles) was refluxed for 2 hours. After cooling, the reaction mixture was hydrolyzed by carefully shaking with water, dried (magnesium sulfate) and the solvent distilled. The oily residue was purified by column chromatography on silica gel using as eluent a mixture of hexane/ether (9:1), to give Va (0.25 g., 68%), m.p. 44-45° (petroleum ether b.p. 40-60°) (Lit. (8) 40-41°).

Butyl 7-Benzoyloxy-2-chromonecarboxylate (Vb).

The compound was prepared from IIIb using the procedure described for Va, yield 63%, m.p. 54-55° (petroleum ether, b.p. 40-60°); ir (cm⁻¹, oil mull): 1735 (ν C=O, ester), 1655 (ν C=O, ketone); pmr: 8.16 center, complex absorption (1H: C₍₅₎H), 7.4 br s (5H: monosubstituted phenyl protons), 7.5 \div 6.9 complex absorption (2H: C₍₆₎H and C₍₈₎H); 7.00 s (1H: C₍₃₎H), 5.18 s (2H: Ar-CH₂-O), 4.45 center, complex absorption (2H: COOCH₂), 2.0 \div 0.8 complex absorption (7H: -CH₂-CH₂-CH₃); uv (methanol, nm): 306 (ϵ = 8,890), 270 (ϵ = 8,230), 241 (ϵ = 18,280).

Anal. Calcd. for C₂₁H₂₀O₅: C, 71.58; H, 5.72. Found: C, 71.36; H, 5.46.

2-Chromonecarboxylic Acid (VIa).

This compound was obtained by hydrolysis of Va in acidic medium according to the described procedure, yield 70%, m.p. 255-256° (Lit. (8) 256-257°).

7-Hydroxy-2-chromonecarboxylic Acid (VIc).

This compound was obtained by hydrolysis of Vb in acidic medium according to the described procedure, yield 70%, m.p. 310° (Lit. (9) 312°).

2'-Hydroxy-2-methoxy-2-methylthioacetophenone (IV) from IIa.

To a solution of IIa (3 g., 15 mmoles) in methanol (75 ml.) were added 10 drops of 10% solution of hydrogen chloride in methanol and the resultant mixture was refluxed under nitrogen for 3 hours. The solvent was then removed by evaporation *in vacuo* and the residual oil solidified by cooling. It was crystallized from 2-propanol to give IV (2.5 g., 78.5%), m.p. 89-90°; ir (cm⁻¹, oil mull): 3100 broad (ν OH phenol), 1645 (ν C=O ketone, chelated); pmr: 7.75 \div 6.50 complex absorption (4H: aromatic protons), 5.04 s (1H: CO-CH-S), 3.45 s (3H: OCH₃), 2.0 s (3H: SCH₃).

Anal. Calcd. for C₁₀H₁₂O₃S: C, 56.58; H, 5.70; S, 15.10. Found: C, 56.56; H, 5.72; S, 14.98.

2'-Hydroxy-2-methoxy-2-methylthioacetophenone (IV) from IIIa.

To a solution of IIIa (5 g., 1.5 mmoles) in methanol (100 ml.) were added 10 drops of 10% solution hydrogen chloride in methanol and the resultant mixture was refluxed under nitrogen for 3 hours. The solvent was distilled *in vacuo* and the residue crystallized from 2-propanol to give IV (2.2 g., 69%), m.p. 89-90°.

Analytical and spectroscopic data were identical with that of compound obtained from IIa as above described.

2-Butoxycarbonylmethylene-3-coumaranone (VIIa).

A solution of a diastereoisomeric mixture of IIIa (5.9 g., 18 mmoles) in dry toluene (80 ml.) and 5 drops of NEP was heated at 60° for 8 hours. After cooling, the solvent was removed by distillation *in vacuo* and the oily residue was purified by column chromatography on silica gel (60 g.) using as eluent a mixture hexane/ethyl ether (98:2) to give VIIa (2.8 g., 45%) as a light-yellow oil. The gas chromatographic analysis (column temperature 190°) showed only a sharp peak with retention time of about four minutes; ir (cm⁻¹, liquid film): 1715 (ν C=O ketone and ester), 1675 (ν C=C); pmr: 7.9 \div 7.1 complex absorption (4H: aromatic protons), 6.17 s (1H: =CH), 4.27 center, complex absorption (2H: COOCH₂), 1.9 \div 0.85 complex absorption (7H: CH₂-CH₂-CH₃); ms: main fragmentation at 246 (M⁺, base peak), 217, 190, 189, 173, 172 and 145 m/e; uv (methanol, nm): 357 (ϵ = 3,710), 263 (ϵ = 13,850, complex band).

Anal. Calcd. for C₁₄H₁₄O₄: C, 68.28; H, 5.73. Found: C, 68.23; H, 5.70.

6-Benzyloxy-2-butoxycarbonylmethylene-3-coumaranone (VIIb).

The compound was prepared from a diastereoisomeric mixture of IVb using the procedure described for VIIa, yielding 44% of VIIb, m.p. 117-118° (isopropyl ether). The gas chromatographic analysis (column temperature 285°) showed only a sharp peak with a retention time of about three minutes; ir (cm⁻¹, oil mull): 1725 and 1710 (ν C=O ester and ketone), 1680 (ν C=C); pmr: 7.8 \div 6.8 complex absorptin (3H: C₍₄₎H, C₍₅₎H and C₍₇₎H), 7.4 br s (5H: monosubstituted phenyl protons), 6.10 s (1H: =CH), 5.17 s (2H: Ar-CH₂-O), 4.25 center, complex absorption (2H: COOCH₂), 1.9 \div 0.8 complex absorption (7H: CH₂-CH₂-CH₃); ms: main fragmentation at 352 (M⁺, base peak), 269, 251, 91 m/e; uv (methanol, nm): 360 sh, 318 (ϵ = 18,150), 272 (ϵ = 16,350), 265

(ϵ = 17,750).

Anal. Calcd. for C₂₁H₂₀O₅: C, 71.58; H, 5.72. Found: C, 71.40; H, 5.51.

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