

Synthesis of Bullatenone and Bullatenone-related Substances

TORSTEN REFFSTRUP and PER M. BOLL

Department of Chemistry, Odense University,
DK-5230 Odense M, Denmark

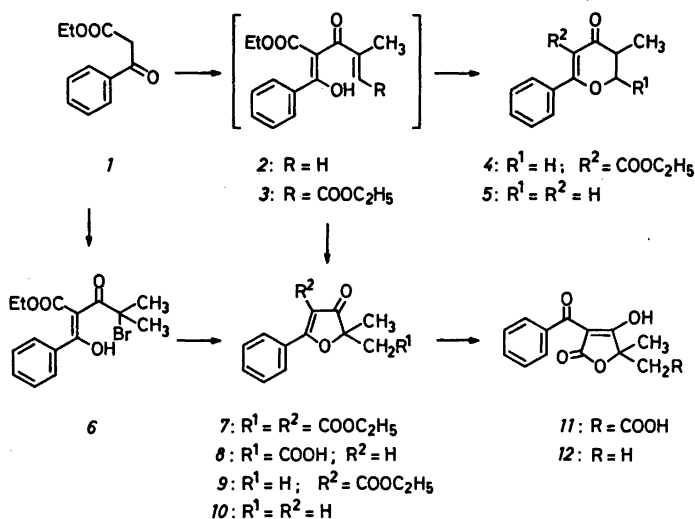
In 1954 an optically inactive unsaturated ketone, bullatenone, was isolated from *Myrtus bullata* and a dihydro- γ -pyrone formulation **5** was proposed for the compound.¹ Subsequently bullatenone was shown to have the structure **10** and its structure was confirmed by synthesis from the not easily accessible 4-hydroxy-4-methyl-1-phenylpent-2-yl-1-one.² Since 3(2*H*)-furanones recently have been considered as potentially useful intermediates for the synthesis of tetrone acids,³⁻⁸ it appeared that routes leading to these intermediates could in principle lead to a facile synthesis of bullatenone. This is, in fact, the case and we here report a facile synthesis of bullatenone and some bullatenone-related substances. The work was performed to make available reference compounds for biosynthetic studies.

One possible route involves cyclisation of (2-alkenyl)-3-keto esters to give either dihydrofuranones^{5,7} or dihydropyrones.^{7,9} Reaction of the ethoxymagnesium salt of ethyl benzoylacetate (**1**) with 1 equiv. of methacryloyl chloride did not result in the isolation of **2**, but gave directly the dihydro-4-pyrone **4**, which could be hydrolyzed and decarboxylated smoothly to **5**, the compound originally thought to be bullatenone.¹ Alternatively, **1** was reacted with *trans*-3-ethoxycarbonylmethacryloyl chloride to give, not **3**, but the desired 3(2*H*)-

furanone **7**. Hydrolysis and decarboxylation resulted in the formation of **8**. Attempts to transform **7** to bullatenone (**10**) were not successful.

The other route used for preparing 3(2*H*)-furanones involves cyclisation of α -haloacyl-3-keto esters.^{3,4,6,8} **1** was reacted with 1 equiv. of 2-bromo-2-methylpropanoyl bromide to give 100% of **6**, which upon cyclisation with triethylamine in toluene afforded 4-ethoxycarbonylbullatenone (**9**). Hydrolysis and decarboxylation of **9** resulted in the formation of bullatenone (**10**). Although no attempt has been made to optimise yields, the latter synthesis constitutes a highly convenient synthesis of bullatenone.

The occurrence of a 3(2*H*)-furanone system in a natural product has apparently not been encountered before and the biosynthesis of bullatenone is, therefore, of interest. Possibly, the biosynthesis can involve reaction of mevalonic acid with a benzoic acid derivative in a not easily explainable manner; but it also seems attractive to consider bullatenone as formed from citraconic or mesaconic acid and a shikimic acid derivative in a manner simulated in the synthesis of **8** from **3** via **7**. The drawbacks of such a biogenetic scheme is that a decarboxylation of **8** to bullatenone (**10**) could not be carried out *in vitro* and that benzoylacetate to our knowledge has not been found in nature. The reasons for taking such a biosynthetic hypothesis into consideration is that 3(2*H*)-furanones carrying a carboxyl group in the 4-position easily can be transformed into tetrone acids (compounds **7** and **9** are transformed with alkali to the tetrone acids **11** and **12**, respectively, in high yields and in almost pure form) and that α -fumaroyl- β -keto esters



via 3(2*H*)-furanones have been transformed directly to naturally occurring tetrone acid fungal metabolites.^{5,7} These latter compounds apparently are biosynthesised from a polyketide and a C₄-compound being either oxaloacetate, fumarate, or malate.¹⁰⁻¹²

Experimental. All m.p.'s and b.p.'s are uncorrected. The ¹H NMR couplings are first order couplings.

Ethyl 5,6-dihydro-5-methyl-4-oxo-2-phenyl-(4*H*)-pyran-3-carboxylate (4). Methacryloyl chloride (26.1 g, 0.25 mol) was added dropwise, at a rate sufficient to maintain vigorous reflux, to a stirred ethereal solution of ethyl ethoxymagnesiobenzoylacetate (prepared⁸ from 48.0 g (0.25 mol) of *I*). The mixture was then refluxed for 30 min, treated at 0°C with ice and 60 ml of 2 M sulfuric acid. The ethereal phase and ether washings of the aqueous phase were dried and evaporated *in vacuo* giving the product as crystals, which upon washing with ether had m.p. 117–119°C (52.6 g, 81%). Anal. C₁₈H₁₆O₄: C, H. UV [ethanol (log ε)]: 217 (3.97), 242 (3.83), 288 (4.20) nm. ¹H NMR (CDCl₃): δ 1.05 (t, 3 H, *J* 7.0), 1.20 (d, 3 H, *J* 6.0), 2.5–3.1 (m, 1 H), 4.11 (q, 2 H, *J* 7.0), 4.0–5.0 (m, 2 H), 7.3–7.8 (aromatic, 5 H).

5,6-Dihydro-5-methyl-2-phenyl-4-pyrone (5). A solution of *4* (5 g, 0.019 mol) in 15 ml of 90% sulfuric acid was heated slowly to 120°C and kept at this temperature until evolution of CO₂ ceased. The solution was poured on ice, and the crystalline material was collected and washed with water to give 3.1 g (87%) of material, m.p. 95–97°C (lit.³ m.p. 96–97°C). UV in agreement with lit.³ ¹H NMR (CDCl₃): δ 1.16 (d, 3 H, *J* 7.0), 2.3–3.0 (m, 1 H), 4.0–4.8 (m, 2 H), 5.97 (s, 1 H), 7.2–7.9 (aromatic, 5 H).

Ethyl (α-bromoisobutyryl)-benzoylacetate (6) was obtained from 2-bromo-2-methylpropanoyl bromide (87.4 g, 0.38 mol) and ethyl benzoylacetate (73.0 g, 0.38 mol) as described for *4*. The product was obtained as a yellow oil (129 g, 100%) and used in crude form (Found: Br 23.0%. Calc. for C₁₈H₁₇BrO₄: 23.4%).

Ethyl 4,5-dihydro-5-ethoxycarbonylmethyl-5-methyl-4-oxo-2-phenylfuran-3-carboxylate (7). Ethyl benzoylacetate (19.2 g, 0.1 mol) and *trans*-β-ethoxycarbonylmethacryloyl chloride (15.8 g, 0.09 mol) were reacted as described for *4*. The combined ether extracts were shaken 5 min with concentrated hydrochloric acid (10 ml), washed twice with sodium hydrogen-carbonate and once with water. After drying (Na₂SO₄) and evaporation of the solvent *in vacuo* 28.4 g of a reddish oil was left. On distillation the fraction with b.p. 180–190°C/0.11 mmHg was collected. Redistillation gave 14.5 g (49%) of yellow oil, b.p. 176–182°C/0.12 mmHg, *n*_D²⁵: 1.5481, UV [ethanol (log ε)]: 213 (4.11), 246 (3.84), 293 (4.20) nm. ¹H NMR (CDCl₃): δ 1.27 (2 × t, 6 H, *J* 7.0), 1.56 (s, 3 H), 2.96 (s, 2 H), 4.20 (2 × q, 4 H, *J* 7.0), 7.3–8.0 (aromatic, 5 H). Anal. C₁₈H₂₀O₆: C, H.

2-Carboxymethyl-2-methyl-5-phenyl-3(2*H*)-furanone (8). Compound *7* (1.0 g, 0.0031 mol) was treated with 90% sulfuric acid as described for *5*, poured on ice and extracted with ether. The ether extracts were dried (Na₂SO₄) and the solvent removed *in vacuo* leaving 0.86 g of viscous oil, which soon solidified. Recrystallisation from ethyl acetate/light petroleum afforded 0.68 g (80%) of colourless plates of m.p. 135–137°C (lit.¹³ m.p. 130–140°C). UV [ethanol (log ε)]: 218 (3.91), 225 (3.88), 240 (3.87), 295 (4.19), 302 (4.20) nm, (lit.¹³ UV [ethanol (log ε)]: 242 (4.02), 295 (4.32), 304 (4.33) nm). The NMR data were in accordance with those published.¹³

Ethyl 4,5-dihydro-5,5-dimethyl-4-oxo-2-phenylfuran-3-carboxylate (9). A mixture of *6* (85.2 g, 0.25 mol) and triethylamine⁸ (50 ml) in dry toluene (700 ml) was stirred at room temperature for 30 min, heated gradually to the b.p. and allowed to cool for 1 h. The precipitate was filtered off and washed with toluene. The toluene phase was evaporated *in vacuo* to give after recrystallisation from tetrachloromethane 27.7 g (43%) of prisms m.p. 60–62°C. Anal. C₁₅H₁₄O₄: C, H. UV [ethanol (log ε)]: 213 (4.12), 247 (3.83), 292 (4.22) nm. ¹H NMR (CDCl₃): δ 1.30 (t, 3 H, *J* 7.0), 1.53 (s, 6 H), 4.28 (q, 2H, *J* 7.0), 7.2–8.0 (aromatic, 5 H).

Bullatenone (10). Hydrolysis and decarboxylation of *9* (5.2 g, 0.02 mol) in 90% sulfuric acid (15 ml) as described for *5* gave 2.9 g (77%) of *10*, m.p. 64.5–67.0°C. On recrystallisation from light petroleum the m.p. was 66–67°C undepressed by admixture with authentic bullatenone. The IR spectra of *10* and authentic bullatenone were superimposable. ¹H NMR (CDCl₃): δ 1.50 (s, 6 H), 5.93 (s, 1 H), 7.3–7.8 (aromatic, 5 H).

3-Benzoyl-5-carboxymethyl-5-methyltetronic acid (11). Compound *7* (1.0 g, 0.0031 mol) was converted to *11* as described.⁷ After work-up the product came out as 0.84 g of oil, which solidified. The crystals were thoroughly ground in ether leaving 0.55 g (65%) of analytically pure *11*, m.p. 140–143°C. Anal. C₁₆H₁₂O₆: C, H. UV [ethanol (log ε)]: 235 (4.32), 283 (4.00) nm. ¹H NMR (CD₃OD): δ 1.56 (s, 3 H), 3.03 (2 × s, 2 H), 7.5–8.3 (aromatic, 5 H).

3-Benzoyl-5,5-dimethyltetronic acid (12). Compound *9* (5.2 g, 0.02 mol) was converted to *12* as described⁷ to give 3.6 g of solidified oil, which upon trituration with ether afforded 3.3 g (89%) of *12*, m.p. 74–75°C. Anal. C₁₃H₁₂O₆: C, H. UV [ethanol (log ε)]: 237 (4.33), 284 (4.00) nm. ¹H NMR (CD₃OD): δ 1.53 (s, 3 H), 1.57 (s, 3 H), 7.4–8.5 (aromatic, 5 H).

Acknowledgement. The authors thank Professor R. A. Raphael for a reference sample of bullatenone and are indebted to Mrs. Irene Mose Andersen for technical assistance.

1. Brandt, C. W., Taylor, W. I. and Thomas, B. R. *J. Chem. Soc.* (1954) 3245.
2. Parker, W., Raphael, R. A. and Wilkinson, D. I. *J. Chem. Soc.* (1958) 3871.
3. Mulholland, T. P. C., Foster, R. and Haydock, D. B. *J. Chem. Soc. Perkin Trans. 1* (1972) 1225.
4. Gelin, S. and Galliaud, A. *C. R. Acad. Sci. Ser. C* (1972) 897.
5. Svendsen, A. and Boll, P. M. *Tetrahedron Lett.* (1974) 2821.
6. Gelin, R., Galliaud, A., Chantegret, B. and Gelin, S. *Bull. Soc. Chim. Fr.* (1974) 1043.
7. Svendsen, A. and Boll, P. M. *J. Org. Chem.* 40 (1975) 1927.
8. Gelin, A. and Hartman, D. *J. Heterocycl. Chem.* 13 (1976) 521.
9. Gelin, S. and Gelin, R. *Bull. Soc. Chim. Fr.* (1968) 288.
10. Lybing, S. and Reio, L. *Acta Chem. Scand.* 12 (1958) 1575.
11. Bentley, R., Bhat, D. S. and Keil, J. G. *J. Biol. Chem.* 237 (1962) 859.
12. Jacobsen, J. P., Refstrup, T. and Boll, P. M. *Acta Chem. Scand. B* 31 (1977) 505.
13. Strunz, G. M. and Kazinoti, P. I. *Can. J. Chem.* 54 (1976) 415.

Received June 20, 1977.

The Reactions of Lignin during Neutral Sulfite Pulping. Part VIII.* Sulfonic Acids Isolated after Treatment of Spruce Wood Meal with Neutral Sulfite

G. GELLERSTEDT and J. GIERER

Swedish Forest Products Research Laboratory,
Chemistry Department, Box 5604, S-114 86
Stockholm, Sweden

The behaviour of the main structural elements of lignin under the conditions of neutral sulfite pulping has been the subject of extensive model experiments.²⁻⁶

The present work is concerned with the isolation and identification of some of the main monomeric sulfonic acids formed during the treatment of finely divided wood with neutral sulfite.

* Part VII, see Ref. 1.

Spruce wood meal (200 g), pre-extracted with acetone, was treated with a solution of sodium sulfite (120 g) in water (1600 ml) at 180 °C for 3 h in a stainless steel autoclave (initial pH ~ 10, final pH ~ 7). The resulting pulp (120 g; lignin content according to Klason 15.7 %) was washed with water and the total liquor concentrated to 2000 ml. Continuous extraction with methylene chloride removed 840 mg of lipophilic material. This was not investigated further. To the remaining aqueous solution, Hyamine 10-X** (80 g) was added to precipitate polymeric lignosulfonic acids.⁷ After centrifugation, tetrabutylammonium sulfate (80 g) was added to the remaining solution. The low-molecular weight lignosulfonic acids were continuously extracted as ion pairs⁸ with methylene chloride. Evaporation of the solvent gave a mixture of sulfonates which were acetylated with acetic anhydride-pyridine (1:1) at room temperature. Excess acetic anhydride and pyridine were removed by evaporation under reduced pressure and water was added. The aqueous suspension was treated with active carbon to remove undissolved material (probably acetylated carbohydrates) and the acetylated sulfonic acids were then converted into methyl esters (23.6 g) as previously⁹ described. Column chromatography on silicic acid (Bio-Sil A 100 - 200 mesh, Bio-Rad Lab., Richmond, California) using ethyl acetate as solvent removed 3.6 g of polymeric material. The remaining low-molecular weight acetylated sulfonic acid methyl esters were separated in a liquid chromatograph (Chromatromix Inc., Berkeley, California) using silicic acid (Bio-Sil A 200 - 325 mesh) as the stationary phase. The flow rate in a 25.4 × 1000 mm column was 1 ml/min. The individual sulfonic acid esters were identified by comparing the ¹H NMR and mass spectra with those of authentic samples (for references, see below).

The mixture of sulfonates was first separated using cyclohexane-ethyl acetate (1:1) as solvent system. Four fractions were obtained in yields of 1.6, 6.2, 2.7 and 4.9 g. On further column chromatography, only fractions 2 and 4 gave pure components. The composition of the other fractions was too complex to allow successful separation.

Fraction 2 (6.2 g) was subjected to chromatography but now using cyclohexane-ethyl acetate (3:2) as solvent system. Five subfractions were obtained in yields of 360, 160, 1060, 945 and 1285 mg.

Subfraction 3 (1.06 g) was further chromatographed using cyclohexane-ethyl acetate (7:3) as solvent system. Pure methyl methanesulfonate⁹ (300 mg) was obtained. ¹H NMR: δ 2.96 (s, 3 H, Me), 3.84 (s, 3 H, OMe).

** Benzyltrimethyl {2-[2-(p-1,1,3,3-tetramethylbutylcresoxy)ethoxy]ethyl}ammonium chloride monohydrate (Rohm and Haas Co.).