787. *The Structure and Synthesis of Bullatenone.*

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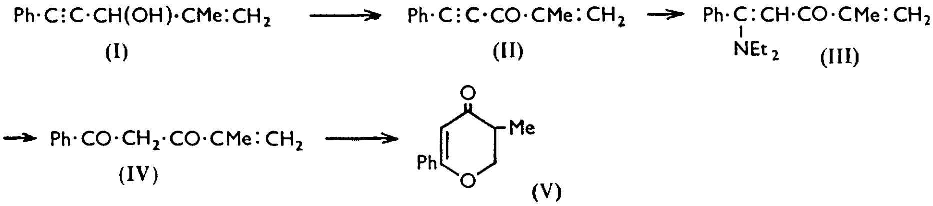
Bullatenone has been shown to be 2 : 3-dihydro-2 : 2-dimethyl-3-oxo-5-phenylfuran (X). This structure has been confirmed by synthesis from 2-methylbut-3-yn-2-ol.

IN 1954 Brandt, Thomas, and Taylor[1] isolated an optically inactive crystalline unsaturated ketone (now named bullatenone) from the blistered-leaf myrtle (*Myrtus bullata*), a shrub endemic to New Zealand. Degradative studies led them to propose the plausible dihydro-γ-pyrone formulation (V) for the compound; the alternative with the methyl group at position 2 was thought less likely but was not conclusively excluded. The main objection to this constitution is the stability of bullatenone to selenium dioxide, a reagent which should readily convert such a compound into the corresponding γ-pyrone.

Both of these dihydro-γ-pyrones have now been synthesised in the following manner. Interaction of 2-methylacraldehyde and phenylethynylmagnesium bromide gave the alcohol (I) which was oxidised to the corresponding ketone (II) with chromium trioxide. Indirect hydration of the triple bond of ketone (II) was achieved by addition of diethylamine and acid hydrolysis of the intermediate enamine (III) to the β-diketone (IV). Initial nucleophilic addition to the triple bond rather than to the similarly activated double bond is predictable from previous work.[2] Cyclisation of the β-diketone (IV) by concentrated sulphuric acid gave the dihydropyrone (V). The corresponding 2-methyl-substituted analogue was obtained in similar fashion by employing crotonaldehyde in the initial condensation. As expected, both of these dihydropyrones were smoothly dehydrogenated to the respective γ-pyrones by selenium dioxide. Neither of the dihydropyrones was identical with bullatenone.



$$\underset{\text{(I)}}{\mathrm{Ph{\cdot}C{:}C{\cdot}CH(OH){\cdot}CMe{:}CH_2}} \longrightarrow \underset{\text{(II)}}{\mathrm{Ph{\cdot}C{:}C{\cdot}CO{\cdot}CMe{:}CH_2}} \longrightarrow \underset{\text{(III)}}{\underset{\mathrm{NEt_2}}{\mathrm{Ph{\cdot}C}}\mathrm{{:}CH{\cdot}CO{\cdot}CMe{:}CH_2}}$$

$$\longrightarrow \underset{\text{(IV)}}{\mathrm{Ph{\cdot}CO{\cdot}CH_2{\cdot}CO{\cdot}CMe{:}CH_2}} \longrightarrow \text{(V)}$$

Owing to the great courtesy of Dr. W. I. Taylor, who not only handed over the problem but also kindly provided us with a generous specimen, we were enabled to re-examine the structure of bullatenone. In carbon tetrachloride the carbonyl stretching frequency appeared at 1705 cm.$^{-1}$ (suggestive of an $\alpha\beta$-unsaturated ketone in a five-membered ring) rather than at the previously reported[1] value of 1681 cm.$^{-1}$ (solid film). The infrared spectrum (KCl pellet) showed further diagnostic absorption at 1604 cm.$^{-1}$ (five-membered cyclic enol ether), 1360 and 1378 cm.$^{-1}$ (CMe_2), and a series of sharp bands appeared between 800 and 1700 cm.$^{-1}$ strongly indicative of the presence of a 2 : 3-dihydro-3-oxofuran system.[3] These results suggested the isomeric structure 2 : 3-dihydro-2 : 2-dimethyl-3-oxo-5-phenylfuran (X) for bullatenone. This formulation explains the resistance of bullatenone to oxidation by selenium dioxide and the lack of optical activity.

This structure was confirmed by synthesis. Reaction of benzaldehyde with the Grignard derivative of 2-methylbut-3-yn-2-ol produced the acetylenic diol (VI), which, by oxidation of the secondary hydroxyl group, furnished the hydroxy-ketone (VII). Addition of diethylamine to the latter, followed by distillation, unexpectedly gave the crystalline

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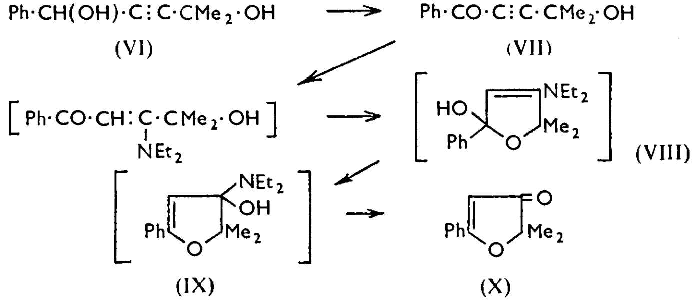
[1] Brandt, Thomas, and Taylor, *J.*, 1954, 3425.

[2] Bowden, Braude, Jones, and Weedon, *J.*, 1946, 45.

[3] Eugster, *Helv. Chim. Acta*, 1957, **40**, 2462.

dihydrofuran (X) directly. A rationalisation of this result can be visualised by an oxotropic rearrangement of the cyclic tautomer (VIII) of the diethylamine adduct followed by the expected ready extrusion of diethylamine from the product (IX). The dihydrooxofuran (X) thus obtained proved identical with bullatenone. The occurrence of this



system in a natural product does not seem to have been encountered before and the biogenesis of bullatenone is not easy to reconcile with either the acetate or the mevalonate hypothesis.

EXPERIMENTAL

2-*Methyl*-5-*phenylpent*-1-*en*-4-*yn*-3-*ol* (I).—Phenylacetylene (30·6 g.) in dry ether (50 ml.) was added to a stirred solution of ethylmagnesium bromide (from magnesium, 7·92 g.) in ether (250 ml.), and the whole heated under reflux, with stirring, for 2 hr. The solution was cooled to −10° and an excess of redistilled 2-methylacraldehyde (24 g.) in ether (75 ml.) was added during 20 min. The mixture was stirred for 2 hr. at room temperature and finally heated to reflux. The cooled mixture was decomposed with 10% v/v aqueous acetic acid (120 ml.), and the ethereal phase was washed with saturated sodium hydrogen carbonate solution and water and dried ($MgSO_4$). Evaporation of the solvent and fractionation of the crude product through a short Vigreux column gave a fore-run of phenylacetylene, b. p. 35—40°/0·07 mm., and then 2-*methyl*-5-*phenylpent*-1-*en*-4-*yn*-3-*ol* as a colourless oil rapidly becoming yellow (35·5 g., 69%), b. p. 104—114°/0·07 mm. The analytical sample had b. p. 100—102°/0·15 mm., n_D^{25} 1·5666, $\lambda_{max.}$ (in chloroform) 250 mμ (ε 14,600) (Found: C, 83·9; H, 7·0. $C_{12}H_{12}O$ requires C, 83·7; H, 7·0%).

2-*Methyl*-5-*phenylpent*-1-*en*-4-*yn*-3-*one* (II).—A stirred solution of the above alcohol (26·3 g.) in acetone (50 ml.) was treated at 0—10° with chromic acid [from chromium trioxide (10·5 g.), water (30 ml.), and concentrated sulphuric acid (8·5 ml.)] during 15 min. Then stirring was continued for another hour at room temperature, and water and ether were next added. The aqueous layer was washed with ether (2 × 100 ml.), and the combined ethereal extracts were washed with dilute sodium hydrogen carbonate solution and dried ($MgSO_4$). Removal of the ether gave the *ketone* as a solid which was purified first by distillation, b. p. 86—110°/0·1 mm. (16·6 g., 63%), and then by crystallisation from aqueous methanol whence it formed prisms, m. p. 54·5—55·5°, $\lambda_{max.}$ (in ethanol) 298 mμ (ε 12,400) (Found: C, 84·8; H, 6·05. $C_{12}H_{10}O$ requires C, 84·7; H, 5·9%).

The 2 : 4-*dinitrophenylhydrazone*, m. p. 200·5—202°, crystallised from chloroform–ethyl acetate in orange platelets, $\lambda_{max.}$ (in chloroform) 268, 300, 384 mμ (ε = 20,200, 9000, and 30,900 respectively) (Found: C, 61·1; H, 3·9; N, 15·2. $C_{18}H_{14}O_4N_4$ requires C, 61·7; H, 4·05; N, 16·0%).

1-*Diethylamino*-4-*methyl*-1-*phenylpenta*-1 : 4-*dien*-3-*one* (III).—Diethylamine (1·5 g.) in ethanol (10 ml.) was added slowly to a stirred solution of the above ketone (3·4 g.) in ethanol (15 ml.) at 0°. The stirring was continued at room temperature for 1 hr. Removal of the ethanol and distillation of the residual syrup furnished the yellow *enamine* (2·12 g., 44%), b. p. 132—136°/0·15 mm., n_D^{25} 1·5830, $\lambda_{max.}$ (in chloroform) 332 mμ (ε 11,900) (Found: C, 79·1; H, 8·45; N, 5·9. $C_{16}H_{21}ON$ requires C, 78·9; H, 8·7; N, 5·75%).

4-*Methyl*-1-*phenylpent*-4-*ene*-1 : 3-*dione* (IV).—The enamine (2·12 g.) was shaken with 2N-sulphuric acid (30 ml.) for 6 hr. and the organic material then isolated by ether. The required *dione* was obtained by distillation as a light yellow oil (0·77 g., 47%), b. p. 98—101°/0·1 mm., n_D^{25} 1·6129, $\lambda_{max.}$ (in *n*-hexane) 225, 245 (inflexion) and 320 mμ (ε 7500, 6800, and 13,300 respectively) (Found: C, 76·6; H, 6·45. $C_{12}H_{12}O_2$ requires C, 76·55; H, 6·45%).

This compound gave a strong colour with aqueous ferric chloride and also formed a copper salt which crystallised from aqueous ethanol in green cubic crystals, m. p. 164°.

2 : 3-*Dihydro*-3-*methyl*-6-*phenyl*-4-*pyrone* (V).—A solution of the above diketone (230 mg.) in concentrated sulphuric acid (3 ml.) was held at room temperature for 24 hr. It was then poured into ice-cold water and extracted with ether, and the ethereal extract washed with saturated sodium hydrogen carbonate solution, then water, and dried ($MgSO_4$). After removal of the solvent the residual red solid was chromatographed in benzene on a short column of alumina (grade III). Elution with chloroform–benzene (1 : 9) and recrystallisation of the isolated product from light petroleum (b. p. 60—80°) afforded the *dihydropyrone* as needles, m. p. 96—97° (100 mg., 43%), $\lambda_{max.}$ (in ethanol) 222, 242, and 296 (ε 8400, 5500, and 17,000 respectively) (Found: C, 76·6; H, 6·1. $C_{12}H_{12}O_2$ requires C, 76·6; H, 6·4%).

The 2 : 4-*dinitrophenylhydrazone* crystallised from ethyl acetate in red needles m. p. 210—212°, $\lambda_{max.}$ (in ethanol) 396 mμ (ε 32,500) (Found: C, 58·95; H, 4·55; N, 15·2. $C_{18}H_{16}O_5N_4$ requires C, 58·7; H, 4·4; N, 15·2%).

5-*Methyl*-2-*phenyl*-4-*pyrone*.—The above dihydropyrone (75·2 mg.) and selenium dioxide (44·4 mg.) were heated under reflux in glacial acetic acid (10 ml.) for 2 hr. The cooled solution was filtered through a pad of " Celite " and evaporated to dryness. The solid residue was dissolved in benzene and adsorbed on a short column of alumina (grade III). Elution with chloroform–benzene (1 : 3) followed by crystallisation of the isolated material from light petroleum (b. p. 60—80°) gave 5-*methyl*-2-*phenyl*-4-*pyrone* in long needles, m. p. 132—133° (42 mg., 56%), $\lambda_{max.}$ (in ethanol) 273 mμ (ε 19,800) (Found: C, 77·4; H, 5·6. $C_{12}H_{10}O_2$ requires C, 77·40; H, 5·4%).

1-*Phenylhex*-4-*en*-1-*yn*-3-*ol*.—Phenylacetylene (30·6 g.) in dry ether (50 ml.) was added to a chilled solution of ethylmagnesium bromide (prepared from magnesium, 7·92 g.), and the solution heated under reflux for 3 hr. Excess of freshly distilled crotonaldehyde (24 g.) in ether (75 ml.) was then added at 0° and the stirring continued for 2 hr. The mixture was worked up as in the above cognate preparation to give the pale yellow *alcohol* (31 g., 60%), b. p 140—146°/0·15 mm., n_D^{23} 1·5850 (Found: C, 83·5; H, 6·85. $C_{12}H_{12}O$ requires C, 83·7; H, 7·0%), $\lambda_{max.}$ (in ethanol) 242 mμ (ε 20,000).

1-*Phenylhex*-4-*en*-1-*yn*-3-*one*.—A stirred solution of the alcohol (26·3 g.) in acetone (50 ml.) was chilled to −10° and treated dropwise with chromic acid [from chromium trioxide (10·5 g.), water (30 ml.), and concentrated sulphuric acid (8·5 ml.)]. The mixture was warmed to room temperature and stirred for 1 hr. Isolation by ether and distillation gave the required *ketone* (16 g., 61%), b. p. 120—124°/1 mm., $n_D^{23·5}$ 1·5938, $\lambda_{max.}$ (in ethanol) 292 mμ (ε 12,200). The 2 : 4-*dinitrophenylhydrazone* crystallised from ethyl acetate in orange-red needles, m. p. 197—198° (Found: C, 61·65; H, 4·05; N, 16·1. $C_{18}H_{14}O_4N_4$ requires C, 61·7; H, 4·05; N, 16·0%)

1-*Phenylhex*-4-*ene*-1 : 3-*dione*.—A solution of diethylamine (1·5 g.) in ethanol (10 ml.) was added dropwise with stirring to the ketone (3·4 g.) in ethanol (15 ml.) at 0°. After 1 hr. at room temperature the solvent was removed and the residue distilled, to furnish the orange diethylamine adduct (3·2 g., 66%), b. p. 136°/0·25 mm., n_D^{24} 1·6031. This adduct (3·4 g.) in acetone (15 ml.) was shaken with 3N-sulphuric acid (30 ml.) for 9 hr., then diluted with water. Isolation with ether gave a yellow semi-solid product (3·15 g.) from which one *isomer* of the dione was isolated by crystallisation from light petroleum (b. p. 30—60°) as needles, m. p. 58—59° (1·7 g.) (Found: C, 76·55; H, 6·5. $C_{12}H_{12}O_2$ requires C, 76·6; H, 6·45%), $\lambda_{max.}$ (in ethanol) 228, 248 (inflexion), 340 mμ (ε 8800, 7400, and 21,800 respectively). This isomer gave a strong red colour with ferric chloride solution, and a copper salt crystallising in plates, m. p. 239—242°, from chloroform–ether. From the mother-liquors a liquid *isomer* (1·4 g.) of the dione was isolated by distillation, having b. p. 102—104°/0·15 mm., n_D^{23} 1·6220 (Found: C, 76·9; H, 6·6%). This isomer gave a strong red colour with ferric chloride, but no copper salt could be prepared.

2 : 3-*Dihydro*-2-*methyl*-6-*phenyl*-4-*pyrone*.—A solution of the above diketone (m. p. 58°) (500 mg.) in concentrated sulphuric acid (6 ml.) was kept at room temperature for 24 hr., then poured on ice and worked up as in the above cognate experiment. The dihydropyrone (263 mg., 53%) crystallised from light petroleum (b. p. 60—80°) in plates, m. p. 62—63° (Found: C, 76·6; H, 6·5. $C_{12}H_{12}O_2$ requires C, 76·6; H, 6·45%), $\lambda_{max.}$ (in ethanol) 222, 242, 298 mμ

(ε 6100, 8000, and 16,900 respectively). Cyclisation of the liquid dione with concentrated sulphuric acid gave the same dihydropyrone, m. p. and mixed m. p. 62°, but in much lower yield.

5-*Bromo*-2 : 3-*dihydro*-2-*methyl*-6-*phenyl*-4-*pyrone*.—The above dihydropyrone (78 mg.) in carbon tetrachloride (10 ml.) was treated with bromine (64 mg.) in carbon tetrachloride for 15 min. at room temperature. After removal of the solvent the mixture was refluxed with collidine (5 ml.) for 15 min., poured into water and extracted with ether, and the ethereal extract was dried ($MgSO_4$). Removal of the solvent gave a brown oil which was chromatographed on a short column of alumina (grade III). Elution with benzene furnished the *bromo-derivative* (36 mg., 35%) which recrystallised in needles, m. p. 106—107° [from light petroleum (b. p. 60—80°)] (Found: C, 54·1; H, 3·95. $C_{12}H_{11}O_2Br$ requires C, 53·8; H, 4·1%), $\lambda_{max.}$ (in ethanol) 306 mμ (ε 11,500).

2-*Methyl*-6-*phenyl*-4-*pyrone*.—2 : 3-Dihydro-2-methyl-6-phenyl-4-pyrone (94 mg.) was refluxed in glacial acetic acid (15 ml.) with selenium dioxide (55·5 mg.) for 2 hr. The cooled mixture was filtered through "Celite," then evaporated to dryness and the residual red solid was chromatographed in benzene on alumina (grade III). Elution with benzene removed traces of selenium; changing the eluant to benzene–chloroform (1 : 1) gave a viscous brown oil (58 mg.) which was sublimed at 110°/0·1 mm. The resulting yellow solid crystallised from light petroleum (b. p. 60—80°) to furnish 2-methyl-6-phenyl-4-pyrone in needles, m. p. 85—86° (lit.,[4] m. p. 83—84°).

4-*Methyl*-1-*phenylpent*-2-*yne*-1 : 4-*diol* (VI).—2-Methylbut-3-yn-2-ol (42 g.) in an equal volume of anhydrous ether was added dropwise to a stirred solution of ethylmagnesium bromide (from magnesium, 24 g.) in dry ether (400 ml.) held at 0°. After 30 minutes' heating under reflux the solution was cooled and treated with benzaldehyde (53 g.) in an equal volume of dry ether, and the mixture refluxed for a further 2 hr. The solid complex which had been precipitated was decomposed with a saturated ammonium chloride solution, the organic layer separated, washed with water, and dried ($MgSO_4$), and the solvent removed to furnish the *diol* as a crystalline mass (74·8 g., 79%). The diol crystallised in needles, m. p. 75—76°, from benzene–light petroleum (b. p. 60—80°) (Found: C, 76·0; H, 7·45. $C_{12}H_{14}O_2$ requires C, 75·75; H, 7·4%).

4-*Hydroxy*-4-*methyl*-1-*phenylpent*-2-*yn*-1-*one* (VII).—A stirred solution of 4-methyl-1-phenylpent-2-yne-1 : 4-diol (19 g.) in acetone (35 ml.) was treated dropwise with a chromic acid solution [from chromium trioxide (7·3 g.), water (20 ml.), and concentrated sulphuric acid (6 ml.)], the temperature of the mixture being held at 0—5°. After one hour's further stirring at room temperature the mixture was diluted with water and extracted with ether (3 × 75 ml.) and the ethereal extract washed with sodium hydrogen carbonate solution and water and dried ($MgSO_4$). Evaporation and distillation furnished the *keto-alcohol* as a pale yellow oil, b. p. 138—139°/0·4 mm., n_D^{22} 1·5529, $\lambda_{max.}$ (in ethanol) 264 mμ (ε 14,700). Treatment with hydrazine sulphate and sodium carbonate by Bowden and Jones's procedure [5] gave the corresponding *pyrazole* which crystallised in needles, m. p. 153—154·5°, from ethyl acetate (Found: C, 71·55; H, 6·75; N, 13·8. $C_{12}H_{14}ON_2$ requires C, 71·3; H, 7·0; N, 13·8%).

2 : 3-*Dihydro*-2 : 2-*dimethyl*-3-*oxo*-5-*phenylfuran* (X).—A stirred solution of the preceding hydroxy-ketone (3·76 g.) in ethanol (20 ml.) was treated dropwise with an ethanolic solution of diethylamine (1·46 g.) and stirring continued for 30 min. Removal of solvent under reduced pressure and distillation gave a yellow oil, b. p. 110°/0·1 mm., which solidified. Crystallisation from light petroleum (b. p. 60—80°) furnished 2 : 3-*dihydro*-2 : 2-*dimethyl*-3-*oxo*-5-*phenylfuran* (1·11 g., 30%) in needles, m. p. 67·5—68·5° undepressed on admixture with bullatenone (Found: C, 76·8; H, 6·7. $C_{12}H_{12}O_2$ requires C, 76·6; H, 6·4%), $\lambda_{max.}$ (in ethanol) 242, 296, 304 mμ (ε 8000, 16,000, and 16,000 respectively). The infrared spectra of substance (X) and bullatenone were superimposable. Modification of the procedure by substituting treatment with dilute sulphuric acid at room temperature for the distillation gave a higher yield (2 g.). The 2 : 4-dinitrophenylhydrazone prepared in the usual manner crystallised from ethanol in dark red needles, m. p. 243—246°, $\lambda_{max.}$ (in ethanol) 412 mμ (ε 26,800); the m. p. was undepressed on admixture with bullatenone 2 : 4-dinitrophenylhydrazone. Treatment of the ketone with bromine in carbon tetrachloride gave the 4-bromo-derivative which was crystallised from light petroleum (b. p. 40—60°) and sublimed at 75°/10^{-4} mm., to yield needles, m. p. 79·5—80·5° (lit.,[1] m. p. 74°)

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[4] Franzosini, Traverso, and Sanesi, *Ann. Chim.* (*Italy*), 1953, **45**, 128.

[5] Bowden and Jones, *J.*, 1946, 953.

(Found: C, 54·15; H, 4·3; Br, 29·9. Calc. for $C_{12}H_{11}O_2Br$: C, 53·95; H, 4·15; Br, 29·75%), $\lambda_{max.}$ (in ethanol) 224, 246, and 314 mμ (ε 6800, 9600, and 16,500 respectively).

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