A NEW HETEROCYCLIC SYSTEM FROM SALOL AND PHENYLACETIC ACID

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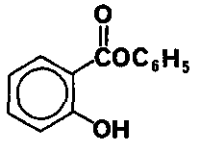
Abstract - Salol when heated with phenylacetic acid gives a compound with a novel heterocyclic system. A sequence by which this new compound may arise is postulated and supported by experiment.

As part of our studies of thermal reactions of salol (1),[1-3] we wish to report that heating it with phenylacetic acid gives three coumarins: The known 3[4] and the new 4 and 5. 4 was an expected product and was readily characterized, but 5, with its unusual structure and new heterocyclic ring, was not. The key to its structure (including its Z configuration) was a ^{1}H NOESY spectrum which showed a very strong NOE between the vinyl hydrogen absorbing at δ6.37 (H-19) and the aromatic proton at δ7.63 (H-14), and a weak but significant NOE between the aromatic protons absorbing at δ7.70 (H-21) and 7.97 (H-5). Somewhat higher yields of 3 and 5 were obtained by heating salol (1) with phenyl phenylacetate rather than with phenylacetic acid.

A reasonable route to 5 involves the sequence 1→2→3→4→5. Support for the view that 4 is an intermediate was gained by heating 4, which we prepared from 3, and obtaining 5 in better yield; the yield of 5 would no doubt have been still higher if the water formed in the reaction had not hydrolyzed much of the starting material 4 back to 3.

Of the many mechanisms which can be envisaged for the 4→5 transformation, the simplest involves bond shifts to give zwitterion 7, which can easily go to 5 by any of several pathways. Alternatively, the reaction may be catalyzed by acid to give protonated 7, or a nucleophile to give an intermediate anion, or may involve an initial [1,5] sigmatropic shift of $C_6H_5CH_2CO$ to give 5 via a different intermediate.



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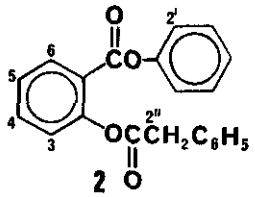

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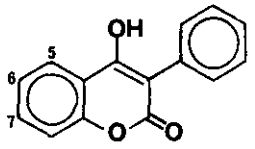

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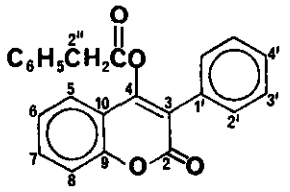

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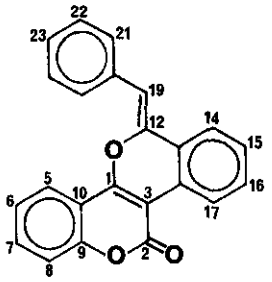

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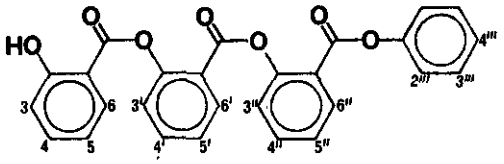

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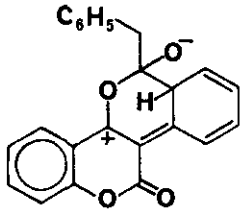

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EXPERIMENTAL

General. Melting points are uncorrected. Nmr spectra were measured at 250 MHz on a Bruker WM-250 spectrometer; 5 was also run at 600 MHz on the Carnegie-Mellon instrument.

Pyrolysis of Salol (1) with Phenylacetic Acid. A mixture of 1 (5.35 g, 25 mmol), phenylacetic acid (3.4 g, 25 mmol), and diphenyl ether (10 ml) was heated at 270°C in a distillation apparatus until 13 ml of distillate was obtained (about 1/2 h). The distillate contained phenol, diphenyl ether, 1, and salicylic acid (800 mg, 23%). The residue (5 g) was chromatographed on silica, eluting with petroleum ether - benzene. In order of elution, the substances identified were diphenyl ether, 1 (547 mg, 10%), phenyl phenylacetate (689 mg, 13%), 2 (1.474 g, 18%, mp 92°C, from petroleum ether; ^{1}H nmr (acetone-d_6) δ3.94 (H-2"), 7.21 (H-2'), 7.2-7.35 (H-3', 4', 4"-6"), 7.46 (H-3), 7.48 (H-5), 7.74 (H-4), 8.19 (H-6), $J_{3,4}$ = $J_{4,5}$ = 7.7, $J_{3,5}$ = 1.1, $J_{4,6}$ = 1.7, $J_{5,6}$ = 7.9 Hz. Anal. Calcd for $C_{21}H_{16}O_4$: C, 75.90; H, 4.82; Found: C, 75.51; H, 4.82), 5 (135 mg, 3%; bright yellow needles, mp 195°C from benzene; ir (nujol) 1635 (C=C) and 1705 (C=O) cm^{-1}; ^{1}H nmr ($CDCl_3$) δ6.37 (H-19), 7.30 (H-23), 7.33 (H-6), 7.34 (H-8 and H-15), 7.41 (H-16), 7.44 (H-22), 7.58 (H-7), 7.63 (H-14), 7.70 (H-21), 7.97 (H-5), 8.85 (H-17), $J_{5,6}$ = $J_{14,15}$ = 8.1, $J_{5,7}$ = $J_{14,16}$ = $J_{21,23}$ = 1.6, $J_{6,7}$ = $J_{16,17}$ = 7.8, $J_{7,8}$ = 8.6, $J_{14,17}$ = 0.5, $J_{15,17}$ = 1.7, $J_{21,22}$ = $J_{22,23}$ = 7.4 Hz; ^{13}C nmr ($CDCl_3$) methinyl carbons δ105.8 (C-19), 116.6 (C-8), 122.8, 123.2, 124.4, 126.0, 127.0, 128.4 and 128.8 (each 2C; C-21 or C-22), 129.1, 130.1, and 132.7 (C-7), and quaternary carbons δ100.9 (C-3), 114.1 (C-10), 125.5, 126.4, 134.3, 146.3 (C-12), 152.7 (C-9), 157.9 (C-4), and 159.3 (C-2). Anal. Calcd for $C_{23}H_{14}O_3$: C, 81.64; H, 4.17; Found: C, 81.64; H, 3.96), 6 (55 mg, 1%; mp 121°C from benzene; ^{1}H nmr ($CDCl_3$) δ6.90 (H-5), 6.98 (H-3), 7.08 (H-2"), 7.19 (H-3"), 7.22 (H-4"), 7.27 (H-3'), 7.36 (H-3"), 7.41 (H-5',5"), 7.48 (H-4), 7.62 (H-4"), 7.65 (H-4'), 8.07 (H-6), 8.22 (H-6"), 8.33 (H-6'), 10.3 (OH), $J_{3,4}$ = $J_{2",3"}$ = 8.5, $J_{3,5}$ = 1.0, $J_{4,6}$ = 1.8, $J_{5,6}$ = $J_{3',4'}$ = $J_{3",4"}$ = 8.1, $J_{3',5'}$ = $J_{3",5"}$ = $J_{2",4"}$ = 1.2, $J_{4',6'}$ = $J_{4",6"}$ = 1.7, $J_{5',6'}$ = 7.9, $J_{5",6"}$ = 7.8 Hz). Anal. Calcd for $C_{37}H_{18}O_7$: C, 71.37; H, 3.96; Found: C, 71.32; H, 4.12), trisalicylide (60 mg, 2%; mp 200°C from benzene, lit. 202-203.5°C[5]; ^{1}H nmr ($CDCl_3$) δ7.42 (H-3), 7.52 (H-5), 7.66 (H-4), 7.98 (H-6), $J_{3,4}$ = 7.7, $J_{3,5}$ = 1.1, $J_{4,5}$ = 8.2, $J_{4,6}$ = 1.7, $J_{5,6}$ = 7.0 Hz; ^{13}C nmr ($CDCl_3$) δ123.8 (C-3), 123.9 (C-1), 126.2 (C-5), 131.8 (C-4), 133.3 (C-6), 148.6 (C-2), 164.7 (C-7). 4 (32 mg, 1%; mp 141°C from ethanol; ^{1}H nmr ($CDCl_3$) δ3.69 (H-2"), 7.12 (H-2'), ~7.24 (H-6,8), 7.31 (H-3',4'), ~7.37 (H-5,4"-6"), 7.58 (H-7); ^{1}H nmr (acetone-d_6) δ3.88 (H-2"), 7.12 (H-2'), 7.28 (H-3',4'), 7.34 (H-6), 7.40 (H-4"-6"), 7.44 (H-8), 7.58 (H-5), 7.69 (H-7), $J_{3,4}$ = 8.4, $J_{3,5}$ = 1.1, $J_{3,6}$ = 0.4, $J_{4,5}$ = 7.3, $J_{4,6}$ = 1.5, $J_{5,6}$ = 7.9 Hz; ^{13}C nmr ($CDCl_3$) δ40.8 (C-2"), 116.1 (C-10), 116.7 (C-8), 120.0 (C-3), 122.8

and 124.4 (C-5,6), 127.6 (C-6"), 128.3 (C-3'), 128.7 (C-4',4"), 129.2 (C-5"), 129.5 (C-2'), 130.1 (C-1'), 131.9 (C-3"), 132.3 (C-7), 152.5 (C-9), 154.8 (C-4), 161.4 (C-2), 167.1 (C-1"). Anal. Calcd for $C_{23}H_{16}O_4$: C, 77.53; H, 4.49; Found: C, 76.81; H, 4.71) and 3 (66 mg, 1%; mp 234°C from ethanol, lit. 231-232°C[4a]; ^{1}H nmr ($CDCl_3$) δ7.92 (H-5), 7.2-7.6 (others), $J_{5,6}$ = 7.8, $J_{5,7}$ = 1.3 Hz). In addition, co-TLC showed the presence of tetrasalicylide (mp 290°C from benzene, lit. 298°C[6]; ^{1}H nmr ($CDCl_3$) δ7.18 (H-3), 7.37 (H-5), 7.60 (H-4), 8.28 (H-6), $J_{3,4}$ = 8.1, $J_{3,5}$ = 1.1, $J_{4,5}$ = 7.6, $J_{4,6}$ = 1.7, $J_{5,6}$ = 7.9 Hz; ms m/z 480 (M+)).

Pyrolysis of Salol (1) with Phenyl Phenylacetate. A mixture of 1 (0.86 g, 4 mmol), phenyl phenylacetate (0.85 g, 4 mmol), and diphenyl ether (10.5 ml) was heated as before. Chromatography of the residue (1.37 g) gave 1 (153 mg, 18%), phenyl phenylacetate (140 mg, 16%), 2 (375 mg, 28%), 3 (64 mg, 7%), 5 (68 mg, 10%), 6 (68 mg, 11%), and trisalicylide (130 mg, 27%). When diphenyl ether was omitted, TLC showed the product distribution to be similar.

3-Phenyl-4-(phenylacetoxy)-coumarin (4) from 3. 3 (150 mg) was converted into 4 (mp 141°C, 135 mg, 60%) by heating with phenylacetyl chloride at 100°C for 1.5 h, washing with $NaHCO_3$, and recrystallizing from ethanol.

5 from 4. 4 (100 mg) was heated slowly in a distillation unit to 265°C. Fractional crystallization of the residue gave 5 (18 mg, 19%) and 3 (43 mg, 64%).

REFERENCES AND NOTES

1. This paper is dedicated to Prof. Alex Nickon on the occasion of his 60th birthday.
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