Preparation and Baeyer-Villiger Oxidation of *ar*-Hydroxy-3-methyl-1-indanones

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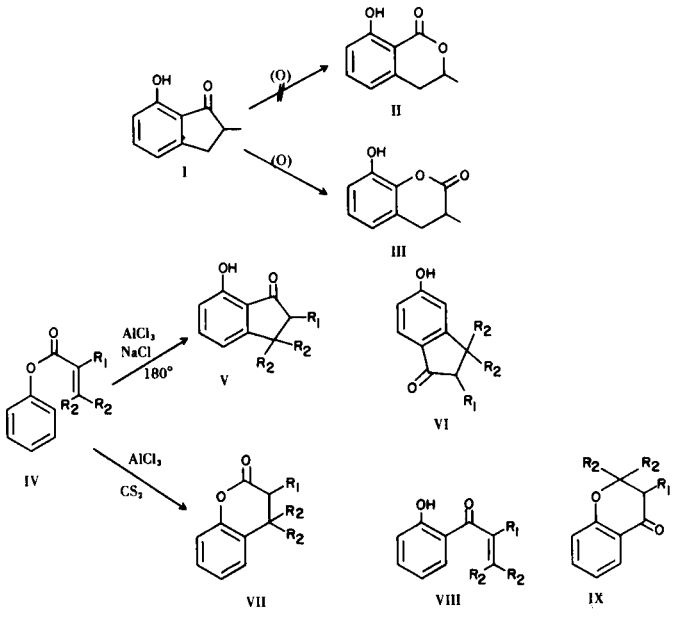
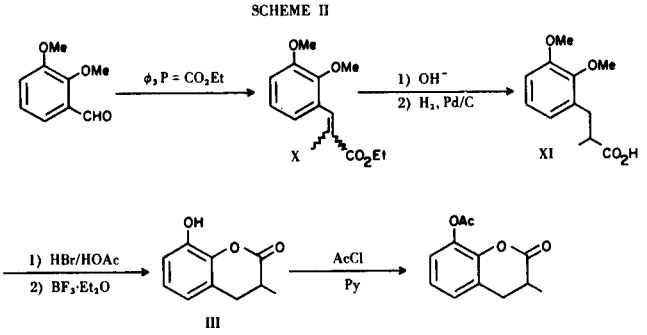
Mellein, II, a metabolic product of various *Aspergillus* fungi (1), has recently been identified as a pheromone secreted by the mandibular glands of male black carpenter ants, *Camponotus pennsylvanicus* (DeGeer), (2). Although a potentially useful synthesis of (±)-mellein has been described (3), we found the procedure difficult to reproduce and sought another approach to the synthesis of II and closely related compounds that might be tested against the ant.

Compound I, 7-hydroxy-2-methyl-1-indanone, was chosen as a synthetic intermediate that would subsequently be subjected to a Baeyer-Villiger oxidation (Scheme 1). The literature does not allow a clear prediction of the migratory aptitudes of secondary alkyl *vs. ortho*-hydroxyphenyl groups, but cyclohexyl migration is favored over phenyl migration by about 5:1 in the peracid oxidation of cyclohexyl phenyl ketone (4). In addition, the Schmidt reaction with 7-methoxyindanones results in alkylmigration (5). We reasoned that if the hydroxyl group were converted to a strongly election-withdrawing substituent, the migratory aptitude of the hydroxyphenyl group should be decreased and that alkyl migration would give the desired dihydroisocoumarin system.

SCHEME I



SCHEME II



Thomson and coworkers (6) described the formation of 7-hydroxy-1-indanones such as V ($R_1 = R_2 = H$) *via* Fries rearrangement of phenyl acrylate in molten aluminum and sodium chlorides. Only the *ortho* migration product (V) was reported. Colonge found earlier that treatment of phenyl β,β-dialkylacrylate, IV ($R_1 = H, R_2 = CH_3$), with aluninum chloride in carbon disulfide produced principally the dihydrocoumarin VII ($R_1 = H, R_2 = CH_3$) accompanied by minor amounts of rearranged but uncyclized α,β-unsaturated ketone, VIII, and by the corresponding chromanone, IX (7). Evidently the course of this reaction is very sensitive to acrylate structure and, perhaps, to reaction conditions. Our interest resided with phenyl methacrylate (IV, $R_1 = CH_3, R_2 = H$), for which no product study has been reported.

Treatment of phenyl methacrylate by Thomson's method gave both the *ortho* and *para* rearrangement products corresponding to structures V and VI, with the latter predominant (~ 3:2). The Fries rearrangement was more conveniently conducted in 1,2-dichloroethane though neither the total yield nor the product ratio were materially altered. Para migration is believed to be intermolecular; *ortho* migration appears to be both inter- and intramolecular (8). Hence, if an α-methyl substituent in the ester moiety imparts some stabilization to an acylium ion, increased *para* migration is not unreasonable. The *ortho* and *para* isomers were easily separated by virtue of the solubility of the *ortho* isomers (the *para* isomers are insoluble) in hot isooctane. In contrast, we found that phenyl cyclopropanecarboxylate heated in the Lewis acid melt rearranged to a mixture of 7-hydroxy-1-indanones in which the 3-methyl isomer predominated over the 2-methyl isomer by ~ 4:1; apparently little or no *para* migration occurred in this case.

The several new indanones were characterized by the usual physical methods, and the structures were confirmed by deuterium exchange (see Experimental).

With I in hand, we now turned our attention to the Baeyer-Villiger oxidation. We felt that trifluoroacetylation of the phenolic oxygen should effectively inhibit aryl migration, but I as its trifluoroacetate proved to be extremely inert to trifluoroperacetic acid and was recovered unchanged (or as the phenol I if an aqueous workup was employed) from several attempted oxidations. Compound I itself was also resistent to the usual Baeyer-Villiger conditions, and more vigorous conditions produced dark mixtures from which no pure compounds were isolated. The acetate of I, on the other hand, reacted rather slowly but cleanly with buffered trifluoroperacetic acid in refluxing methylene chloride to give the acetate of the 3,4-dihydrocoumarin III in 88% yield. The structure of this compound was confirmed by a more conventional synthesis as illustrated in Scheme II. Thus in spite of the presence of the acetate group, only aryl migration had occurred. Similarly, trifluoroperacetic acid oxidation of the acetate of VI (R_1 = CH_3, R_2 = H) also gave the product of aryl migration.

Aryl migration therefore appears to be the rule in the peracid oxidation of 7-(and 5)-acetoxyindan-1-ones. Since the Baeyer-Villiger oxidation did proceed cleanly and in high yield, albeit in the direction opposite to the one anticipated, this method does appear to provide a useful route to oxygenated 3,4-dihydrocoumarins.

EXPERIMENTAL (9)

General.

Melting points were determined on a Fisher-Johns apparatus and are uncorrected. Ir spectra were recorded by a Perkin-Elmer 457 A Grating Infrared Spectrophotometer. Nmr spectra were determined with a Varian T-60 spectrometer, and uv data were obtained with a Beckman DK-2A Ratio Recording Spectrophotometer.

Gas chromatographic analyses were performed on Hewlett-Packard 5700A and Varian Aerograph 1520B instruments equipped with an SE-30 column (0.92 m x 0.63 cm 5% on Anakrom ABS) and a HI-EFF column (1.22 m x 0.63 cm 5% on Anakrom ARS).

Deuterium exchanges were performed by heating the indanones with sodium carbonate-deuterium oxide at 170° for 5 hours in sealed tubes.

Fries Rearrangement of Phenyl Methacrylate.

A. Aluminum Chloride in 1,2-Dichloroethane (DCE).

Phenyl methacrylate (0.10 mole) and aluminum chloride (0.20 mole) were heated under reflux in DCE (250 ml.) for 16 hours. The reaction mixture was cooled, poured over cracked ice, and extracted with ether. The phenols were extracted from the ether with 1 *N* potassium hydroxide and were recovered from the aqueous phase by acidification (hydrochloric acid) and extraction with ether. The ether phase was dried (magnesium sulfate) and concentrated. The residue was extracted with boiling isooctane (3 x 25 ml.). The insoluble material (7.1 g. 44%) was identified as 5-hydroxy-2-methyl-1-indanone (VI, R_1 = CH_3, R_2 = H); the isoctane extract upon concentration and steam distillation provided 3.6 g. (22%) of 7-hydroxy-2-methyl-1-indanone (V, R_1 = CH_3, R_2 = H).

Compound V (R_1 = CH_3, R_2 = H) had; ir (carbon tetrachloride): 3360s (hydrogen bonded OH, sharpness indicative of intramolecularity) 1685s, 1627, 1607 cm^{-1}; nmr (carbon tetrachloride): δ 1.27 (d, J = 7, 3, CH_3), 2.4-3.0 (m, 2, CH_3CH and one benzylic H), and 3.32 ppm (q, J = 8 and 17, one benzylic H). Hydrogen-deuterium exchange removed the proton *alpha* to the carbonyl and converted the CH_3 to a singlet, and the benzylic protons now appeared as a AB quartet at 2.58 and 3.32 ppm. The 2,4-DNPH (orange) had m.p. 258° dec.

Anal. Calcd. for $C_{16}H_{14}N_4O_5$: C, 56.14; H, 4.12; N, 16.37. Found: C, 56.31; H, 4.12; N, 16.33.

Compound VI (R_1 = CH_3, R_2 = H) had m.p. 159-160° (water); ir (chloroform): 3240 (broad), 1685, 1595 cm^{-1}; nmr (DMSO-d_6): δ 1.15 (d, J = 7, 3, CH_3), 2.4-2.9 (m, 2, CH_3CH and one benzylic H), 3.33 ppm (q, J = 9 and 17, one benzylic H), nmr (1:1 deuteriochloroform-DMSO-d_6): after hydrogen-deuterium exchange, same observations as for V (R_1 = CH_3, R_2 = H), AB quartet at 2.58 and 3.52 ppm; uv (ethanol): λ max 203 (12700), 223 (11900), 269 (11700), 292 (11200) nm; 2,4-DNPH (red) had m.p. 280° dec.

Anal. Calcd. for $C_{16}H_{14}N_4O_5$: C, 56.14; H, 4.12; N, 16.37. Found: C, 56.24; H, 3.96; N, 16.27.

B. Molten Aluminum and Sodium Chlorides.

Phenyl methacrylate (0.5 ml.) was added to a mixture of aluminum chloride (2 g.) and sodium chloride (0.5 g.) in a test tube which was then heated in an oil bath at 110° for 1.5 hours. The reaction mixture was worked up essentially as in A and gave ~0.15 g. of V and 0.25 g. of VI (R_1 = CH_3, R_2 = H). Simialr results were obtained at 170° for 2 minutes or at 160° for 2.5 hours.

Fries Rearrangement of Phenyl Cyclopropanecarboxylate.

A mixture of the ester (2.0 g.), aluminum chloride (16 g.), and sodium chloride (4 g.) was heated at 150-165° for 2 hours and then worked up as described for A to give 1.2 g. of a liquid containing 7-hydroxy-2-methyl-1-indanone (V, R_1 = CH_3, R_2 = H) and the isomeric 7-hydroxy 3-methyl-1-indanone. Preparative glc (HI-EFF column) provided a sample of the 3-methyl isomer: ir (carbon tetrachloride): 3340s, 1685, 1625, 1605, 1415, (CH_2C=O) cm^{-1}; nmr (carbon tetrachloride): δ 1.38 (d, J = 7, 3, CH_3), 2.17 (q, J = 3.5 and 18, one benzylic H), 2.85 (q, J = 7 and 18, one benzylic H), 3.1-3.5 (m, 1, CH_3CH) ppm, nmr after hydrogen-deuterium exchange: absence of benzylic protons, retention of methyl doublet, methine quartet at 3.68 (q, J = 7, 1, CH_3CH); semicarbazone, m.p. 172-174° (ethanol-water):

Anal. Calcd. for $C_{11}H_{13}N_3O_2$: C, 60.28; H, 5.95; N, 19.17. Found: C, 60.45; H, 6.07; N, 18.93.

Preparation of the Acetates of V and VI (R_1 = CH_3, R_2 = H).

The hydroxyindanone, 10 mmoles and 12.5 mmoles of triethylamine were stirred in 40 ml. of anhydrous ether. Acetyl chloride (10 mmoles), was added dropwise to the cooled (10°) mixture. The mixture was refluxed for 4 hours, cooled, and diluted with cold water. The aqueous phase was washed with ether, and the combined organic phase was washed sequentially with 1*N* potassium hydroxide, dilute hydrochloric acid and water. After drying (magnesium sulfate), the solvent was removed, and the product was crystallized from petroleum ether. Yields were nearly quantitative, and infrared and nmr data were in accord with the assigned structure.

Acetate of V (R_1 = CH_3, R_2 = H): an oil used directly in the Baeyer-Villiger oxidation.

Acetate of VI (R_1 = CH_3, R_2 = H) had m.p. 59-60° (ethyl acetate-pentane).

Anal. Calcd. for $C_{12}H_{12}O_3$: C, 70.57; H, 5.92. Found: C, 70.66; H, 5.86.

Baeyer-Villiger Oxidations of the Acetates of V and VI (R_1 = CH_3, R_2 = H).

The acetoxyindanone (1.55 mmoles) was added to a suspension of disodium hydrogen phosphate (5.05 mmoles) in dichloromethane (15 ml.). A solution of trifluoroperacetic acid in dichloromethane (1.9 ml. of 1.5 mmoles per ml.) was added, and the resulting mixture was refluxed overnight. The mixture was diluted with ether and washed with aqueous sodium bicarbonate. The organic phase was dried (magnesium sulfate) and concentrated to give the corresponding acetoxylactone in 80-85% yield.

Acetate of III, m.p. 104-105° (ethyl acetate-hexane); ir (chloroform): 1700 cm^{-1}; nmr (deuteriochloroform): δ 1.32 (d, J = 7, 3 CH_3), 2.30 (s, 3, CH_3C=O), aryl protons appear as a broad singlet at 7.00 ppm; uv (ethanol): λ max 193 (13900), 254 (1800), sh 263 (1600).

Anal. Calcd. for $C_{12}H_{12}O_4$: C, 65.44; H, 5.49. Found: C, 65.35; H, 5.47.

6-Hydroxy-3-methyl-3,4-dihydroisocoumarin Acetate.

This compound had m.p. 94.94.5° (ethyl acetate-cyclohexane); ir (chloroform); 1770 cm^{-1}; nmr (carbon tetrachloride): δ 1.08 (d, J = 6, 3, CH_3), 2.00 (s, 3, CH_3C=O), 6.65 (s, 3, aryl protons) ppm. uv (ethanol): λ max 201 (16700), 216 (10600), 258 (1300), sh 265 (1100).

Anal. Calcd. for $C_{12}H_{12}O_4$: C, 65.44; H, 5.49. Found: C, 65.60; H, 5.55.

Preparation of Ethyl 3-(2,3-Dimethoxyphenyl)-2-methylacrylate (X).

Sodium ethoxide (freshly prepared from 25 mmoles of sodium hydride), and methyl carboethoxymethyltriphenylphosphonium bromide (25 mmoles) obtained as an oil from ethyl 2-bromopropionate and triphenylphosphine in acetonitrile) were added to dry DMF (30 ml.) under nitrogen. After 15 minutes 2,3-dimethoxybenzaldehyde (2.5 g.) was added and the mixture was allowed to stand overnight; then it was diluted with water and extracted with ether. The crude product was extracted with isooctane and carried forward without further purification: nmr (carbon tetrachloride): δ 1.30 (t, J = 7, 3, CH_3CH_2), 1.95 and 1.97 (3, allylic CH_3-mixture of geometrical isomers), 3.73 (s, 3, OCH_3), 3.78 (s, 3, OCH_3), 4.18 (q, 2, GH_3CH_2) ppm.

Preparation of 3-(2,3-Dimethoxyphenyl)propionic Acid.

The crude ester, X, was heated under reflux in a solution of potassium hydroxide (0.1 mole) in 50% aqueous ethanol (30 ml.) for 2 hours. The mixture was concentrated, diluted with water, and extracted with ether. The aqueous phase was acidified (hydrochloric acid) and extracted with ether. The extract was dried (magnesium sulfate) and concentrated to give 1.65 g. of solid acid. This material was hydrogenated at atmospheric pressure in absolute ethanol (40 ml.) with 5% Pd on charcoal (150 mg.) for 16 hours. The product, XI, was recovered in the usual fashion and was an oil: nmr (carbon tetrachloride): δ 1.13 (d, J ~ 7, 3, CH_3), 3.77 (s, 6, OCH_3), 6.70 (m, 3, aryl protons) ppm.

Conversion of XI to III (R_1 = CH_3, R_2 = H).

The acid XI (4.5 mmoles) was added to a mixture of 5 ml. each of hydriodic and acetic acids, and this mixture was heated at 80-100° for 16 hours. The mixture was diluted with water and extracted with ether. The product at this stage was only partially lactonized and was therefore dissolved in boron trifluoride etherate (10 ml.) for 2 hours at ambient temperature. The product was recovered in standard fashion to give 0.5 g. (63%) of III, m.p. 96-97.5° (sublimation), ir (chloroform) 3600, 1770b, 1625, 1610 cm^{-1}.

Anal. Calcd. for $C_{10}H_{10}O_3$: C, 67.40; H, 5.67. Found: C, 67.68; H, 5.83.

This compound was converted to its acetate as previously described and found to be identical in all respects with the Baeyer-Villiger oxidation product from the acetate of V (R_1 = CH_3, R_2 = H).

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(9) Mention of a proprietary product in this paper does not constitute an endorsement of this product by the USDA.