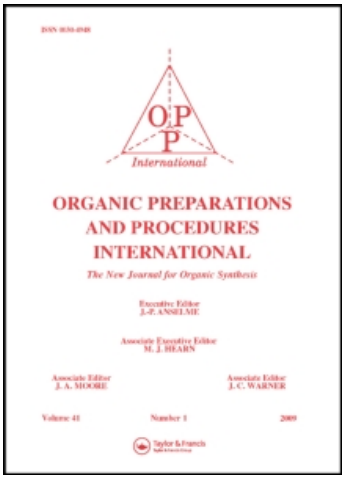

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AN IMPROVED SYNTHESIS OF 3-*N*-PENTADECYL CATECHOL (3-PDC)

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AN IMPROVED SYNTHESIS OF 3-n-PENTADECYL CATECHOL (3-PDC)

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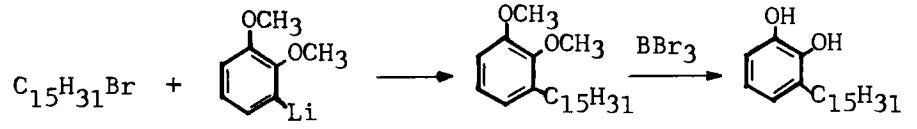
3-n-Pentadecyl catechol (3-PDC, III), the saturated component of the poison ivy principle, is in constant demand as a standard allergen[1-7] in the clinical diagnosis of poison ivy allergy. It is a colorless solid that is much easier to produce and handle in pure form than the olefinic components of poison ivy Urushiol. It has also been in demand as a starting material[8-10] for the laboratory preparation of a variety of analogs designed to unravel the mystery behind the phenomena of delayed hypersensitivity and immunologic tolerance.



I II III

Although 3-PDC has been synthesized previously in five ways,[1,11-14] only two are practical routes,[11,13] both of which are multi-step syntheses requiring special skills and equipment. The most widely used synthetic route to 3-PDC, prior to the present investigation, involves a four-step reaction sequence[13] starting from the commercially available

compound o-vanillin. The entire synthesis is usually accomplished in about two weeks' time, requiring a pressure shaker machine and other sophisticated glass apparatus. A troublesome and technically demanding terminal step is involved.

In the present investigation, the synthesis of the intermediate, 3-n-pentadecyl veratrole (II), was accomplished in a single step from 1-bromopentadecane (I), involving a substantial modification of the procedure previously reported by Byck and Dawson.[15] The proportions of the reagents and the reaction conditions have been studied and optimized for speed and economy. The incorporation of a tetrahydrofuran-anhydrous ether solvent system[16] in the ratio 6:5 has been found to reduce the metalation reaction time considerably and result in a significant improvement in the yield.

The main problem in the synthesis of 3-PDC has always been in the cleavage of the methyl ethers of II. The presence of a long hydrocarbon chain ortho to the ether grouping often caused incomplete ether cleavage. Thus, while veratrole can be cleaved completely to catechol by conventional reagents such as hydroiodic acid, more drastic conditions were found necessary for the cleavage of 3-n-pentadecyl veratrole and its homologs. The high temperature required for complete cleavage prevented the synthesis of a number of heat-labile derivatives of 3-PDC via 3-n-pentadecyl veratrole.[10]

A noteworthy reaction, the cleavage of a 3-n-alkyl veratrole II by boron tribromide,[17] has been investigated in these laboratories. The merits of this reagent are apparent. The only apparatus required is an ordinary round-bottomed flask equipped with a magnetic stirrer and a drying tube. The reactants are simply mixed and stirred at room temperature. At this temperature there is no need for an inert atmosphere. Most importantly, despite the presence of a long alkyl side-chain, ether cleavage was found to be complete even at room temperature. The amount of technical skill and attention required is minimal, but the yield and purity of the product are equal to or better than any other methods of cleavage previously used.

This two-step synthesis lasts only four days, with the third day being a waiting period for the second reaction. The overall yield of pure 3-PDC is 67%, which is significantly higher than the overall yields of the earlier methods.

The boron tribromide cleavage has been applied to the synthesis of 4-piperidinomethyl-3-n-pentadecyl catechol hydrochloride and its 5-piperidinomethyl isomer.[18] In all cases, ether cleavage was complete, and high yields of pure products were obtained.

EXPERIMENTAL

Melting points were taken on a Thomas-Hoover capillary melting point apparatus and are corrected. Infrared spectra were determined on a Jasco IRA-1 diffraction grating infrared spectrophotometer, and were measured in carbon tetrachloride solution. The NMR spectra were obtained with a Varian T-60 spectrometer using tetramethylsilane as an internal standard and carbon tetrachloride as solvent. Elemental analyses were performed by Micro-Tech Laboratories, Skokie, Ill.

3-n-Pentadecyl veratrole (II). - To a solution of 35.7 g (0.258 mol) of veratrole[19] in 138 mL of tetrahydrofuran (THF) under a nitrogen atmosphere was added, with stirring and ice-bath cooling, 115 mL (0.172 mol) of a 1.50 M solution of n-butyllithium[20] in anhydrous ether during 30 min. The mixture was stirred at 0° for 2 hrs and then refluxed for 0.5 hr to complete the reaction and destroy any unreacted n-butyllithium. A solution of 26.1 g (0.0900 mol) of 1-bromopentadecane[19] in 27 mL of THF was added to the yellow suspension during 15 min. The mixture was refluxed overnight (17 hrs). After cooling in an ice-bath, the mixture was treated with 100 mL of 10% hydrochloric acid. The layers were separated. The aqueous layer was extracted with 100 mL of ether. The combined organic solution was washed first with 10% aqueous sodium hydroxide to remove phenolic side-products, then with brine. After drying over anhydrous magnesium sulfate, the solvents were evaporated, leaving a yellow oil which was subjected to vacuum distillation. A 23.5 g yield (75%) of II, slightly contaminated with veratrole, was collected at 177° (0.30 Torr). Recrystallization from 95% ethanol afforded in about 65% yield a high purity 3-n-pentadecyl veratrole, mp. 36.0-

37.0°, lit.[13] mp. 36.2-36.7°, indistinguishable in IR and NMR from an authentic sample.

3-n-Pentadecyl catechol (III)[21]. - To a solution of 16 g (0.064 mol) of boron tribromide[22] in 50 mL of benzene was added with stirring, a solution of 10.0 g (0.0287 mol) of II in 200 mL of benzene during 30 min. The yellow mixture, protected from ingress of moisture by a calcium chloride drying tube, was stirred at room temperature for 24 hr. Then 200 mL of air-free water (flushed with pure nitrogen) was added, and the layers were separated. The aqueous layer was extracted with ether. The combined organic solution was washed with air-free water, dried over anhydrous magnesium sulfate, and the solvents were removed. The brown residue was distilled at 0.15 Torr to yield 8.28 g (90%) of 3-PDC, bp. 176°, mp. 59.5-61.0°, lit.[13] mp. 59.0-60.0°. The IR and NMR spectra of III were identical to those of an authentic sample.

Anal. Calcd for $C_{21}H_{36}O_2$: C, 78.69; H, 11.32. Found: C, 78.66; H, 11.57.

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