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SYNTHESIS AND BIOLOGICAL ACTIVITY OF NOVEL BUTYL PARABEN DERIVATIVE

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ABSTRACT

Parabens are class of chemicals widely used as preservatives in the cosmetic and pharmaceutical industries. They are effective preservatives in many types of formulas. These compounds and their salts are used primarily for their bacterial and fungicidal properties. They are also used as food additives. Their analogues *viz.* ethers, esters and hybrid / fused molecules also possess various biological activities which prompted us to synthesize few more analogues for their future application as bioactive molecules. The synthesized compound was unambiguously characterized by IR, ^{1}HNMR, Maas and elemental analysis.

KEYWORDS: parabens, IR, ^{1}HNMR, Mass, elemental analysis and hybrid molecule, antibacterial, Gram + ve and Gram - ve bacteria *etc*.

INTRODUCTION

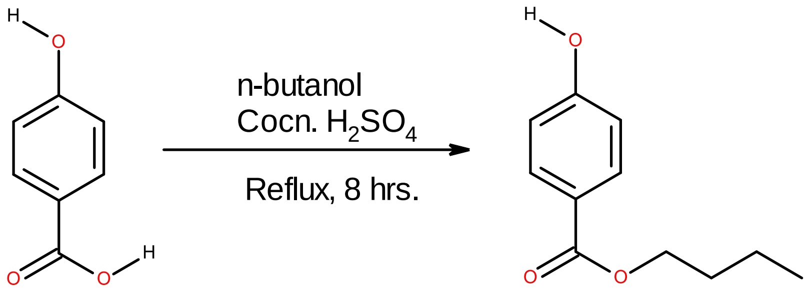
Phenolic phytochemicals are known to exhibit anti-inflammatory, antioxidant, anticarcinogenic, antidiabetic, antiatherosclerosis and immunomodulatory activities in animals[1,2]. These are mostly polyphenols known as secondary plant metabolites[3] present in plant and trees. One of such compound is 4-hydroxy benzoic acid which is used as antifungal, antimutagenic, antisickling, esterogenic[4] and antimicrobial[5] agent. It is primarily known as the basis for the preparation of its esters, known as parabens, which are used as preservatives in cosmetics. Parabens are used for their bactericidal and fungicidal properties. They can be found in shampoos, commercial moisturizers, shaving gels, personal lubricants, topical / parenteral pharmaceuticals, spray tanning solution, makeup and toothpaste. They are also used as food additives. In the present study, we are converting 4-hydroxy benzoic acid to butyl paraben using conventional method and their further diversification to ester derivative. It is an antimicrobial preservative used in many cosmetics, as a food flavoring agent and as a suspending agent for medications. Since butyl paraben is naturally occurring active compound having antioxidant and antimicrobial properties, we decided to make a library of compounds[6-8] using various permutation and combinations to come up with novel ether, ester and hybrid derivatives of butyl paraben using conventional methods. The objective of this study is to condense two molecules of the same disease domain to produce more potent candidate in the same disease domain or to condense two molecules of different disease domain to produce mixed variety of those disease domain or to have drug candidate with entirely different biological activity. In the present work, we are converting 4-hydroxy benzoic acid to butyl paraben which in turn further converted to its hybrid derivative using conventional method and tested for its potential antibacterial activity.

RESULTS AND DISCUSSION :

Preparation of Butyl Paraben:- It was prepared by refluxing 4–hydroxy benzoic acid (25 gms) with n-butanol (250 ml) using sulphuric acid (1 ml) as a catalyst for 8 hrs. The progress of the reaction was monitored by TLC for the completion of reaction.

Work up :- The reaction mixture concentrated under reduced pressure to minimum and to that 200 ml of dichloromethane + 200 ml of water was added. The aqueous layer was extracted successively with dichloromethane (2 x 100 ml). The total organic layer was washed with water (200 ml), brine (100 ml) and concentrated to yield butyl paraben quantitatively (33.75 gms, 96 %).

Reaction Scheme :



(1)

4-hydroxybenzoic acid

(2)

butyl 4-hydroxybenzoate

The above procedure can be scaled up to get more quantities of butyl paraben.

Butyl-4-hydroxybenzoate (2)

^{1}H NMR (500 MHz, $CDCl_3$) δppm : 0.985 (t, J = 7.5 Hz, 3H, terminal $–CH_3$ from butyl paraben moiety), 1.4 – 1.6 (m, 1 x $–CH_2$, 2H, $-CH_2$ from butyl paraben moiety), 1.7 – 1.8 (m, 1 x $–CH_2$, 2H, $-CH_2$ from butyl paraben moiety), 6.41 (brs, 1H, -OH, D_2O exchangeable), 7.256 (d, J = 9.0 Hz, 2H, ortho coupling, ArH from butyl paraben moiety), 8.105 (d, J = 9.0 Hz, 2H, ortho coupling, ArH from butyl paraben moiety); TOF MS ES : 195 (M + H), 217 (M + Na); Molecular formula $C_{11}H_{14}O_3$; Colourless, odorless crystalline powder (26.4 gms, 96.0 %). Melting range 68 – 69^0 C; Anal. Calcd. For $C_{11}H_{14}O_3$: C 68.0 % H 7.30 % O 24.70 %. Found : C 67.98 % H 7.28 % O 24.72 %;

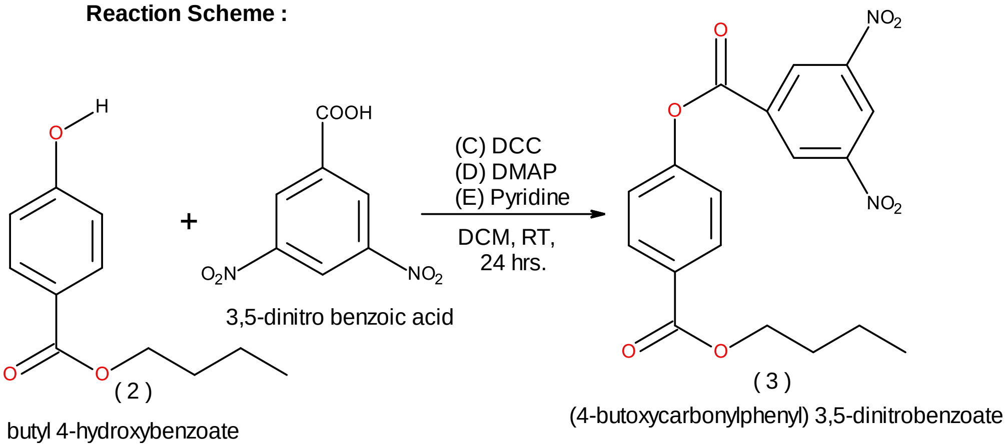
Butyl paraben was then subsequently converted to its hybrid derivative as mentioned below.

Diversification of butyl paraben to its hybrid derivative (3) :- This was prepared by following general method as depicted below.

To a stirred solution of [A] (1 eq.) in 40 ml dichloromethane was added [C] (1.4 eq.), [D] (0.05 eq.), [E] (4 drops) and stir the reaction mixture at room temperature for 5 min. Clear solution of reaction mixture was obtained. To this, compound [B] (1.4 eq.) was added and stirring continued at room temperature for next 8 hr. As the reaction proceeds, urea derivative precipitates out as by product. The progress of the reaction was monitored by TLC for the completion of reaction.

Work up :- The reaction mixture filtered through Buchner funnel, wash the cake with 10 ml of dichloromethane. This gets rid of byproduct urea derivative. The total organic layer was concentrated to minimum, preadsorbed on silica gel (100 – 200 mesh) and purified by column chromatography with increase in concentration of ethyl acetate in petroleum ether. The general yields of these reactions ranges between 70 – 80 %.

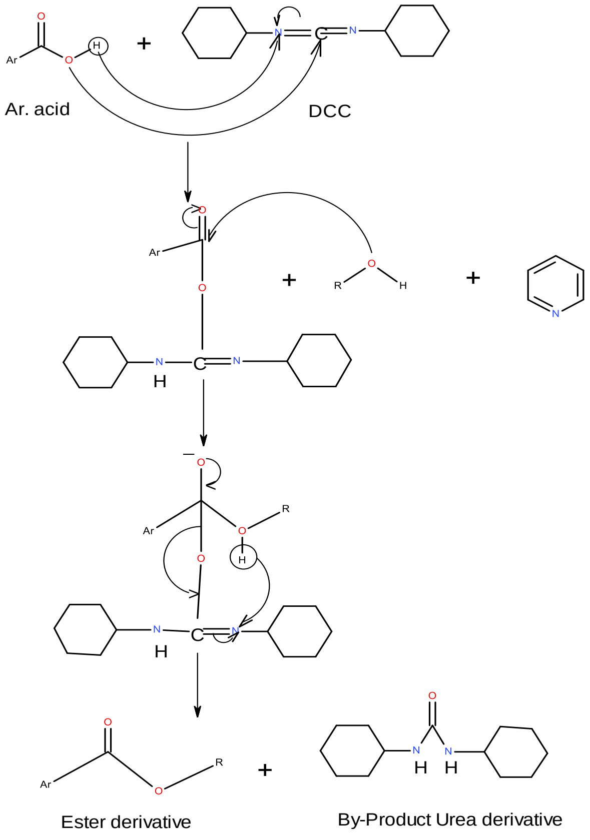
Reaction Scheme :



Compound No.	IUPAC Name
3	(4-butoxycarbonylphenyl)-3,5-dinitrobenzoate

The general mechanism for this reaction can be given as follows.

Probable mechanism for fused / hybrid molecules :



(4-butoxycarbonylphenyl)-3,5-dinitrobenzoate (3)

^{1}H NMR($CDCl_3$, 500 MHz) δ ppm :- 1.002 (t, *J* = 8.0 Hz, 3H, terminal $–CH_3$ from butyl paraben moiety), 1.4 – 1.6 (m, 1 x $–CH_2$, 2H, $-CH_2$ from butyl paraben moiety), 1.7 – 1.9 (m, 1 x $–CH_2$, 2H, $-CH_2$ from butyl paraben moiety), 4.358 (t, *J* = 7.0 Hz, 2H, $-OCH_2$ from butyl paraben moiety), 7.365 (dd, *J* = 8.0 Hz, 2.5 Hz, 2H, ArH, ortho as well as meta coupling from butyl paraben moiety), 8.178 (dd, *J* = 8.5 Hz & 2.5 Hz, 2H, ArH, ortho as well as meta coupling from butyl paraben moiety), 9.325 (d, *J* = 2.0 Hz, 3H, ArH meta coupling from 3,5-dinitro benzoic acid); IR (KBr) cm^{-1} : 2957 – 2864 (methyl, methylenes and methines), 1749 - 1713 (ester >C=O), 1605 (Aromatic); TOF MS ES : 372 (M), 373 (M + H); Molecular Formula $C_{18}H_{16}N_2O_8$; Pale yellow solid (1.40 g, 82 %); Melting range 64 – 65^{0}C; Elemental Analysis, Calcd : C 55. 70 % H 4.20 % N 7.2 % O 33.00 % Found C 55.68 % H 4.18 % O 33.03 %;

^{1}H NMR Analysis : The peak resonating at 1.002 *ppm* appeared as a triplet integrating for three protons corresponding to terminal methyl group from butyl paraben moiety. The peaks resonating at 1.4 – 1.6 ppm & 1.7 – 1.9 ppm appeared as a multiplate integrating for 4 protons corresponding to two methylene groups from butyl paraben moiety. The peak at 4.358 ppm appears as a triplet integrating for two protons corresponds to $–OCH_2$ group from butyl praben moiety. Such a deshielding is due to CH_2 group is attached to electronegative oxygen bonded carbon. The peak resonating at 7.365 ppm integrating for two protons appeared as a double doublet with *J* = 8.0 Hz & 2.5 Hz corresponding to ortho and meta coupling from butyl paraben moiety. The signal appeared at 8.178 ppm with *J* = 8.5 Hz & 2.5 Hz integrating for two protons corresponding to *ortho* and *meta* coupling from butyl paraben moiety. The signal resonated at 9.328 ppm appeared as a doublet integrating for three protons with *J* = 2.0 Hz corresponding to *meta* coupling from 3,5-dinitrobenzoic acid moiety.

IR Analysis : In original Butyl Paraben, tertiary phenolic –OH group appears at 3379 cm^{-1}. Similarly, in original 3,5-dinitrobenzoic acid, the acid carbonyl appears at 1706 cm^{-1} as sharp peak. However, when condensation reaction is carried out between Butyl Paraben and 3,5-dinitrobenzoic acid using DCC as a dehydrating agent, the peak at 3379 cm^{-1} corresponding to tertiary phenolic –OH and acid carbonyl peak at 1706 cm^{-1} disappears and peak due to ester carbonyl at 1749 cm^{-1} appears with the elimination of water molecule suggesting that reaction takes place at this position resulting in the formation of desired ester molecule. The peaks appearing at 2957 – 2864 cm^{-1} corresponding to methyls, methylenes and methines from both the aromatic moieties. The peak at 1605 cm^{-1} accounts for the presence of aromatic moiety.

The most significant features of this methodology are (a) good accessibility of the reagent and its stability (b) a stoichiometric amount of reagent can be used by direct weighing, avoiding excess (c) no evolution of hazardous vapours during the reaction (d) the total elimination of the use of toxic organic solvents (e) a simple experimental procedure (g) good control over the outcome of the reaction by varying the amount of reagent (h) less expensive and (i) very simple reaction work up with avoidance of by-product. The aforesaid protocol thus provides an improved procedure for the synthesis of useful hybrid derivatives having important pharmaceutical, agricultural and other physicochemical properties.

EXPERIMENTAL

Melting points were determined on a Thomas Hoover capillary melting point apparatus using digital thermometer. IR spectra were recorded on a Shimadzu FTIR Prestige model as KBr pellet. ^{1}H NMR spectra was recorded on a Varian 500 MHz spectrometer in $CDCl_3$. Chemical shifts were recorded in parts per million using tetramethyl silane as standard. Mass spectra was recorded on a TOF MS ES mass spectrometer. Elemental analysis were carried out as a percentage on a Thermo finnigan, Flash EA 1112 series, Italy.

CHROMATOGRAPHIC SYSTEM

Column chromatography: For column chromatography 100 – 200 mesh Acme grade silica gel is used. The crude reaction mixture is concentrated under reduced pressure to yield crude mass which is preadsorbed on silica gel and purified by column chromatography with increase in concentration of Ethyl acetate in Petroleum ether. The fractions having similar ‘rf’ values were pooled together, concentrated and subjected for characterization using various spectroscopic techniques.

Thin layer chromatography: TLC plates were prepared using silica gel G (ACME, BOMBAY). Pet. ether: EtOAc (85: 15) was used as the solvent system.

Radial chromatography: The circular glass plates of thickness 1 mm, were prepared by using silica gel (PF254, E. MERCK, 50 g) in cold distilled water (105 ml). For elution, gradually increasing concentrations of EtOAc in pet ether were employed.

BIOLOGICAL ACTIVITY:

Antibacterial Activity using ditch plate method[10]:-

The synthesized molecule was screened for its potential antibacterial activity using ditch plate method at 100 µg/ml concentration against Gram positive and Gram negative bacterial species qualitatively. The results of the antibacterial activities are summarized in **Table 1**.

Theory : One of the many ways to test the anti-bacterial activity of compounds / drugs is ditch plate method. Ditch plate method is a preliminary method to screen the test compounds / drugs for their potential as antimicrobials. In this method, the compound to be tested for antimicrobial activity is seeded in the agar plate and the test organisms are streaked across.

PROCEDURE: A ditch 10 mm wide is cut into sterile MH agar plate. The test drug / compound is added to 5 ml molten MH agar butt at 40^{0}C and this mixture is poured into the ditch and allowed to solidify. The ditch should be made in level with the rest of the agar by pouring the mixture . The different bacterial cultures are streaked perpendicular to the ditch using nichrome wire loop. The plate is then incubated at 37^0 C for 24 hours.

The results are observed as inhibition of bacterial growth on the ditch as well as adjacent to the ditch.

RESULTS: The following test samples showed anti-bacterial activity against the organisms mentioned in the following Table.

SAMPLE NO.	ACTIVE AGAINST
PCMX	*Staphylococcus aureus* [Gram positive] *Salmonella typhi* [Gram negative] *Klebsiella pneumoniae* [Gram negative] *Corynebacterium diphtheriae* [Gram positive] *Escherichia coli* [Gram negative]
Std. Drug Ampicillin	*Staphylococcus aureus* [Gram positive] *Salmonella typhi* [Gram negative] *Klebsiella pneumoniae* [Gram negative] *Corynebacterium diphtheriae* [Gram positive] *Escherichia coli* [Gram negative]
3	*Staphylococcus aureus* [Gram positive] *Corynebacterium diphtheriae* [Gram positive] *Klebsiella pneumoniae* [Gram negative] *Salmonella typhi* [Gram negative]

The above results shows that the base molecule PCMX has anti-bacterial activity against both the bacterial cultures. Its derivatives viz. 3 was also active against specific Gram + ve and Gram - ve cultures as mentioned in the above table.

CONCLUSION

The novel ester derivative of butyl paraben was synthesized by cost effective industry viable process following the principle of green chemistry. The synthesis of ester derivative is achieved using DCC as dehydrating agent in a reasonably good yield. The probable mechanism for the formation of ester derivative was also discussed. The synthesized compound was totally new as confirmed from Scifinder search.

In depth analysis of these compounds through structure activity relationship studies would provide further insight and can be an interesting topic of future studies.

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