Indian Journal of Chemistry
Vol. 61, January 2022, pp. 88-93

Investigation of the antimicrobial and anticorrosive properties of new pyridinium derivatives on the basis of the Mannich phenolic bases

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Received 27 April 2020; accepted (revised) 26 October 2021

Herein is reported the synthesis and investigation of novel pyridine-based quaternary ammonium salts of phenol derivatives, obtained using the Mannich reaction. The biological activity of the synthesized compounds has been investigated against gram-negative *E. coli* and gram-positive *S. aureus* bacteria and *C. albicans* and *A. niger* fungi. In addition to this, their anticorrosive properties have also been investigated.

Keywords: Pyridine, quaternary ammonium salt, phenol derivatives, biological activity, anticorrosive properties

As known from the literature[1–3] in this field, phenol motifs prevail in a wide spectrum of natural products, drugs, dyes and industrially important materials, and they represent the perfect sustainable class of starting materials for diversified modes of bond construction in chemical and material sciences. As a result, the site-selective functions of phenols are highly desirable and widely used all over the world[1]. One of the most important phenol functions is the synthesis of ortho-aminomethylated phenol structures by the Mannich reaction, which has various applications such as in biologically active components[4], ligands for transition metals[5], catalysts or components of catalysts[6–8], saluretic agents[9], inhibitors of carbonic anhydrase I and II isoenzymes[10], multifunctional additives for lubricating oils[11] and intermediates in organic synthesis[12–14].

Heterocyclic compounds attract the attention of researchers due to their broad range of applications, and therefore, there is continued interest in the development of practical methods for their assembly[15]. Pyridine and its derivatives, as representatives of heterocycles, are worthy of attention for many reasons, chief among which are their biological activities. The biological activities of these molecules show antimicrobial[16,17], antiviral[18–20], antioxidant[21], antidiabetic[22], anticancer[23,24], antimalarial[25], anti-inflammatory[26,27], anti-amoebic[28] and enzyme-inhibiting[29] properties among others. The derivatives of pyridines with applications in medicine include nifedipine, amlodipine, nimodipine, lercanidipine and others[30]. Another positive aspect of these compounds is that they are excellent herbicides and pesticides. They also have applications in the textile industry and related fields. Furthermore, they are also used as chemical processing aids (acid acceptors) and as industrial corrosion inhibitors[31]. Some success was achieved in the development of N-butyl pyridinium nitrate and N-hexylpyridinium nitrate as ionic liquids in green chemistry, proving these to be effective solvents in the process of extracting toluene from a mixture of alkanes under atmospheric conditions[32]. In addition to this, it is also possible to synthesize various calixarenes[33] on the basis of them as well as various macrocyclic derivatives with unusual and extraordinary properties that are applied in material sciences[34].

Considering the importance of ortho-aminomethylated phenols and pyridine derivatives, we carried out the Mannich reaction for the synthesis of ortho-aminomethylated phenols, based on which new pyridine-based quaternary ammonium salts were synthesized. Taking into account the wide spectrum of applications of these type of compounds, we investigated their biological activity against gram-negative E. coli and gram-positive S. aureus bacteria and C. albicans and A. niger fungi. Moreover, their anticorrosive properties were also investigated and promising results were obtained.

Materials and methods

All the chemicals applied in the synthesis were purchased from Sigma-Aldrich (Taufkirchem,

Germany) and used as received. The control of the reaction's progress and determination of the synthesized compounds' purity levels were attained using TLC on Sorbfil plates with iodine vapors as the developer. The melting points were recorded in open capillary tubes on a Buchi B-540 apparatus and remained uncorrected. Elemental analysis was performed using the Carlo Erba 1108 analyzer.

NMR spectra

The NMR experiments were performed using a BRUKER FT NMR spectrometer AVANCE 300 (Bruker, Karlsruhe, Germany) (300 MHz for 1 H and 75 MHz for 13 C) with a BVT 3200 variable temperature unit in 5-mm sample tubes and the Bruker Standard software (TopSpin 3.1). The 1 H and 13 C chemical shifts were referred to as internal tetramethylsilane (TMS); the experimental parameters for 1 H were as follows: digital resolution = 0.23 Hz, SWH (spectral width in Hz) = 7530 Hz, TD (time domain) = 32 K, SI (Fourier transform size) = 16 K, 90 pulse-length = 10 ms, PL1 (power level for F1 channel) = 3 dB, ns (number of scans) = 1, ds (number of dummy scans) = 0, d1 (relaxation delay) = 1 s; and the parameters for 13 C were as follows: digital resolution = 0.27 Hz, SWH = 17985 Hz, TD = 64 K, SI = 32 K, 90 pulse-length = 9 ms, PL1 = 1.5 dB, ns = 50, ds = 2, d1 = 3 s. The NMR-grade D_2O (99.7%; 0.3% H2O) was used for the solutions of 8, 9, 10 and 11.

IR spectra

FTIR spectra were recorded on a Varian 3600 FTIR spectrophotometer in KBr tablets. The spectra were taken in the range of 4000-400 cm^{-1} at room temperature.

Experimental synthesis procedure

The synthesis of compounds 1, 2 and 3 using the Mannich reaction and further ethers of 4, 5, 6 and 7 on the basis of the aforementioned compounds were carried out according to the literature[35].

The aminomethylation reaction of the phenols was carried out according to a known method involving the interaction of equimolar amounts of phenol, formaldehyde (37% aqueous solution) and amines (according to Mannich) as follows: The reaction was carried out in a three-necked flask equipped with a stirrer, thermometer, reflux condenser and dropping funnel. The calculated quantities of amine and formalin (36% aqueous formaldehyde solution) were loaded into the flask. After thorough mixing, the temperature was increased from 35 to 55°C (depending on the nature of the amine taken). When the flask was brought down to room temperature, calculated amounts of alkenylphenol were added to the mass through a dropping funnel. The mass was mixed at a temperature of 70–75°C for 4–5 hours. Upon the completion of the reaction, the organic portion was extracted with benzene or toluene and dried over Na_2SO_4. The aminomethyl derivatives of the alkenylphenols were isolated from the mass by vacuum distillation (at a pressure of 1–3 mm) or by transferring them to their corresponding quaternary ammonium salts upon treatment with hydrogen chloride and subsequent decomposition with aqueous ammonia.

Synthesis of bromine-containing ethers based on aminomethylated phenols

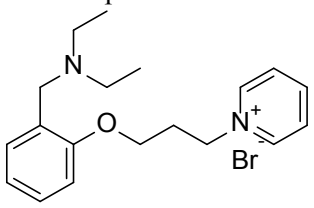
In a mixture containing 3 g (0.022 mol) of phenol, 1.2 g (0.022 mol) of KOH, and 0.05 g of KI (promoter) solvent, 7.32 g (0.03 mol) of 1.6-dibromhexane dissolved in 20 ml of isopropanol was added while stirring. The mass was stirred at a temperature of 80ºC for 4 hours. Upon the completion of the condensation process, the mixture was separated from the KBr by decantation, and the solvent was removed using a rotary evaporator. Then, under a vacuum (at a pressure of 1-3 mm), 2-oxyhexamethylene bromide was distilled off in the form of a viscous mass of light yellow color (Typ 103–105ºC / 3 mm). Yield 50% of theory, $nD201.5375$.

The condensation of 5 g (0.05 mol) of aminophenol with 10 g (0.075 mol) of 1,6-dibromhexane in isopropanol (20 ml) was carried out under similar conditions. After the appropriate treatment (distillation of isopropanol in a rotary evaporator) and vacuum distillation, the viscous substance (bpc 113ºC / 3 mm) of $nD201.5375$ 2-hydroxyhexamethylene bromide was obtained. Then, through its interaction with pyridone (in acetonitrile medium), a compound was obtained.

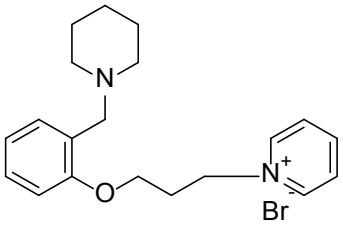
Synthesis of novel pyridine-based quaternary ammonium salts (8–11)

To a mixture of subsequent bromide (4–7) in 150 ml of acetonitrile, 5 g (0.063 mol) of freshly distilled pyridine was added while stirring. The mass was stirred at a temperature of 80ºC for 7 hours. The

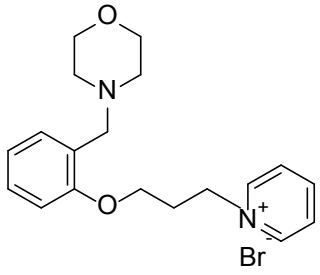
solvent was removed from the reaction product using a rotary evaporator. The target compounds were white solids, which were then purified under a high vacuum.



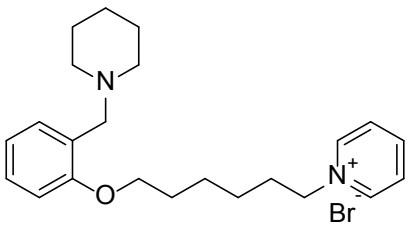
Yield 70.5%, m.p. 225ºC. ^{1}H NMR-spectrum of the 2-diethylaminomethylphenoxypropylpyridini-um bromide (8): (D_2O, δ, м.д.), 1.0-1.3 t (6H, $2CH_3$), 1.9 m (2H, CH_2), 2.1 s (2H, CH_2), 3.0-3.3 q (4H, $2CH_2$), 4.0 t (2H, CH_2), 4.3 s (2H, CH_2), 7.0-7.5 m (9H, Ar). ^{13}C NMR-spectrum of the 2-diethylaminomethy lphenoxypropylpyridinium bromide: (D_2O, δ, м.д.), 8 ($2CH_3$), 22 (CH_2), 54 ($2NCH_2$), 58 (CH_2Ar), 58.8 (CH_2N), 75 (CH_2O), 122 (CH, Ar), 123 (2CH, Ar), 125 (2CH, Ar), 133 (2CH, Ar), 134 (2CH, Ar), 158 (C, Ar), 162 (C, Ar). Looking at the FTIR spectrum of compound 8, the peaks within the range 1631-1296 cm^{-1} are corresponding to stretching vibrations of C-C in aromatic ring. The peaks within the range 1195-1018 cm^{-1} are corresponding to deformation vibrations of CH groups in the plane of aromatic ring. The band at 1241 cm^{-1} corresponds to stretching vibration of C_{Ar}-OCH_2 group. Found, %: C 60.07; H 7.09; N 7.34; $C_{19}H_{27}N_2BrO$. Calculated, %: C 60.16; H 7.17; N 7.38.



Yield 87.1%, m.p. 241ºC. ^{1}H NMR spectrum of 2-piperidinomethylphenoxypropyl pyridinium bromide (9): (D_2O, δ, м.д.), 1.0-2.0 m (8H, $4CH_2$), 2.5 s (2H, CH_2), 3.1-3.5 t (6H, $3CH_2$), 4.2 t (2H, CH_2), 6.8-7.6 m (9H, Ar). ^{13}C NMR spectrum of 2-piperidinomethyl phenoxypropyl pyridinium bromide: (D_2O, δ, м.д.), 15 (CH_2), 20 (CH_2), 21 ($2CH_2$), 46 ($2NCH_2$), 56 (CH_2Ar), 58.6 (CH_2N), 69.6 (CH_2O), 123 (2CH, Ar), 127 (2CH, Ar), 128 (C, Ar), 139 (CH, Ar), 139.3 (CH, Ar), 142 (CH, Ar), 148 (CH, Ar), 150 (CH, Ar), 158 (C, Ar). Looking at the FTIR spectrum of compound 9, the peaks within the range 1630-1286 cm^{-1} are corresponding to stretching vibrations of C-C in aromatic ring. The peaks within the range 1184-1011 cm^{-1} are corresponding to deformation vibrations of CH groups in the plane of aromatic ring. The band at 1245 cm^{-1} corresponds to stretching vibration of C_{Ar}-OCH_2 group. Found, %: C 61.45; H 6.91; N 7.11; $C_{20}H_{27}N_2BrO$. Calculated, %: C 61.38; H 6.95; N 7.16.



Yield 85%, m.p. 230ºC. ^{1}H NMR-spectrum of the 2-morpholinomethylphenoxybuthyl pyridinium bromide (10): (D_2O, δ, м.д.), 1.9-2.1 m (4H, $2CH_2$), 2.4 s (2H, CH_2), 3.1-3.6 m (4H, $2CH_2$), 3.9 t (2H, CH_2), 4.5 m (6H, $3CH_2$), 7.1 s (1H, Ar), 7.9 s (3H, Ar), 8.5 s (2H, Ar), 8.7 s (3H, Ar).^{13}C NMR-spectrum of the 2-morpholinomethylphenoxybuthyl pyridinium bromide: (D_2O, δ, м.д.), 23 (CH_2), 23.2 (CH_2), 47 ($2NCH_2$), 56 (CH_2Ar), 56.6 (CH_2N), 62 (CH_2O), 62.2 ($2CH_2O$), 123 (2CH, Ar), 123.3 (2CH, Ar), 128 (C, Ar), 139 (2CH, Ar), 139.3 (CH, Ar), 142 (2CH, Ar), 157 (C, Ar). Looking at the FTIR spectrum of compound 10, the peaks within the range 1632-1292 cm^{-1} are corresponding to stretching vibrations of C-C in aromatic ring. The peaks within the range 1172-1031 cm^{-1} are corresponding to deformation vibrations of CH groups in the plane of aromatic ring. The band at 1242 cm^{-1} corresponds to stretching vibration of C_{Ar}-OCH_2 group. Found, %: C 58.09; H 6.45; N 7.15; $C_{19}H_{25}N_2BrO_2$. Calculated, %: C 58.02; H 6.41; N 7.12.



Yield 88%, m.p. 235ºC. ^{1}H NMR-spectrum of 2-piperidinomethylphenoxyhexyl pyridinium bromide (11): (D_2O, δ, м.д.), 1.0-2.0 m (14H, $7CH_2$), 2.5 s (2H, CH_2), 3.1-3.6 t (6H, $3CH_2$), 4.1 t (2H, CH_2), 6.6-7.6 m (9H, Ar). ^{13}C NMR-spectrum of 2-

piperidinomethylphenoxyhexyl pyridinium bromide: (D_2O, δ, м.д.), 15 (CH_2), 16 (CH_2), 17 (CH_2), 19 (CH_2), 20 (CH_2), 21 ($2CH_2$), 47 ($2NCH_2$), 57 (CH_2Ar), 59.9 (CH_2N), 70.6 (CH_2O), 124 (2CH, Ar), 126 (2CH, Ar), 128 (C, Ar), 139 (CH, Ar), 139.7 (CH, Ar), 142.1 (CH, Ar), 147 (CH, Ar), 150 (CH, Ar), 159 (C, Ar). Looking at the FTIR spectrum of compound 11, the peaks within the range 1636-1262 cm^{-1} are corresponding to stretching vibrations of C-C in aromatic ring. The peaks within the range 1169-1015 cm^{-1} are corresponding to deformation vibrations of CH groups in the plane of aromatic ring. The band at 1228 cm^{-1} corresponds to stretching vibration of C_{Ar}-OCH_2 group. Found, %: C 63.79; H 7.74; N 6.52; $C_{23}H_{33}N_2BrO$. Calculated, %: C 63.74; H 7.67; N 6.46.

Biological activity

Strains of cultures of S. aureus ATCC®25923; E. coli ATCC®25922, C. albicans ATCC®90028 as well as A. niger mold isolates (isolated from drinking water and food) were used in this work. BD Mueller Hinton broth, Mueller Hinton agar, Saburo agar, BBLTL Coagulase Mannitol agar and Endo agar were used as nutrient media. At the first stage of the study of antibacterial properties, serial dilutions of the liquid media (or the suspension method) were used to establish the minimum inhibitory concentration (MIC) of the investigated compound for an isolated strain of the microorganism. The observation was carried out at different exposure times: 30 min, 60 min, 120 min and 240 min. Based on the results, which were expressed in CFU/ml, the inhibitory activity of the investigated compound was evaluated. Solutions of 100 μg/ml (without dilution) and 10 μg/ml (with dilution of 1:10), 1 μg/ml (of 1:100), 0.1 μg/ml (of 1:1000) and 0.01 μg/ml (of 1:10000) in relation to the strains of E. coli, S. aures, C. albicans and A. niger were prepared.

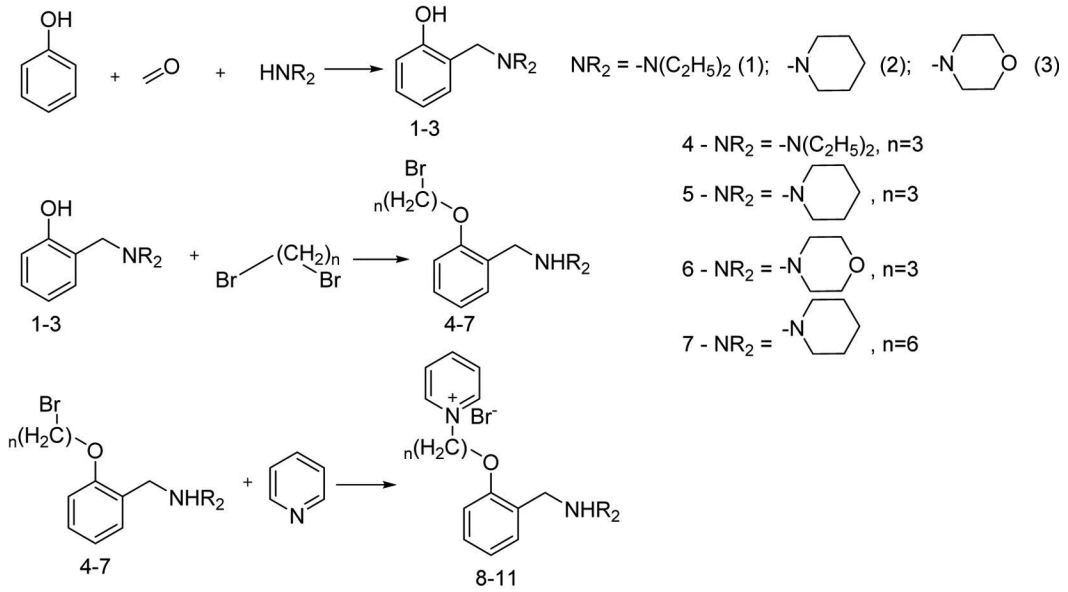
In the second stage, the disk-diffusion method was used on the selected media for each pathogen. The initial concentration of the sample was 1 mg/ml (1000 μg), followed by dilutions of 100 μg, 10 μg, 1 μg and 0.1 μg.

Equal volumes of microbial flora (1 ml each) were layered on Petri dishes with a selected medium using a standard inoculum. Ajar cups were dried in a box at room temperature for 15 minutes. Then, in laboratory settings, sterile disks of various concentrations were prepared. The plates were incubated in a thermostat for 24 hours at 37°C. The degree of sensitivity of the microorganism to the synthesized substance was determined by the width of the inhibition growth in mm.

Results and Discussion

First, our investigations began with the synthesis of ortho-aminomethylated phenols using the Mannich reaction, and compounds 1–3 were obtained. Next, phenol ethers were synthesized based on ortho-aminomethylated phenols and dialkylbromides, which resulted in compounds 4–7. Subsequently, pyridine-based quaternary ammonium salts were synthesized, and compounds 8–11 were obtained with good yields (Scheme I).

Considering the broad range of biological activity



Scheme I — Synthesis of compounds **1-11**

Table I — Antimicrobial activity of compound **9** and **10** against *E.coli* and *S.aureus*

Compd	The inhibition zone, mm		Concentration,
Microorganisms	*E.coli*	*S. aureus*	mg/ml
	16	20	1,0
9	10	15	0,1
	8	12	0,01
	6	10	0,001
	17	18	1,0
10	12	14	0,1
	9	10	0,01
	7	8	0,001

Table II — Antimicrobial activity of compound **9** and **10** against *C.albicans* and *A.niger*

Compd	The inhibition zone, mm		Concentration,
Microorganisms	*C. albican*	*A. niger*	mg/ml
	18	16	1,0
9	14	13	0,1
	10	11	0,01
	15	10	1,0
10	12	8	0,1
	9	6	0,01

investigations and analyzed the antimicrobial activity of compounds 9 and 10 against both gram-positive (S. aureus) and gram-negative (E. coli) bacteria and fungi (C. albicans and A. niger). The result of this analysis by the serial dilution method allowed us to determine the MIC of the investigated compounds; in the case of both the compounds, it was 0.001 mg/ml against both bacteria and 0.01 mg/ml in the case of fungi. Further, we performed an analysis using the disk diffusion method. According to this analysis, the activity of compound 10 was higher in the case of E. coli, whereas compound 9 demonstrated higher activity against S. aureus. The same trend was not observed with the fungi. Compound 9 was found to be more active against both the fungi compound 10 (Table I and Table II).

It is known that quaternary pyridinium compounds occupy an important place among water-soluble metal corrosion inhibitors. Due to the presence of surface-active anions (Cl-, Br-, Y-, etc.) in their structures as well as an organic cation, the metal's surface has high adsorption properties that contribute to effectively protecting it against corrosion and can often lead to internal synergism. Considering this, the quaternary pyridinium salts 8, 9 and 10 obtained from aminomethylated derivatives of phenols were studied as water-soluble inhibitors in the 3% aqueous solution–hydrocarbon (kerosene) medium (1:9 wt.). The concentration of the inhibitors was 50 and 100 mg/l. The tests were carried out on steel 3 at room temperature for 5 hours. Compound 10 was found to have the highest corrosion efficiency, while the lowest was in the case of Compound 8 (Table III).

Table III — Anticorrosion activity of compounds **8**, **9** and **10** in aqueous solution–hydrocarbons (kerosene) medium

Compd	Concentration mg/L	Corrosion rate (g/m^2 h)	Corrosion efficiency (%)
8	50	5.264	88
	100		
9	50	5.376	92
	100		
10	50	5.488	96
	100		
Without inhibitor	–	2,8	–

Conclusion

Compounds 8–11, the new derivatives of the pyridine-based quaternary ammonium salts, were synthesized, and their structures were investigated using spectroscopic methods. Considering that the proposed substances, being pyridine derivatives, may have the ability to act as antimicrobial drugs, they were tested for the biological activity against gram-negative E. coli and gram-positive S. aureus bacteria and C. albicans and A. niger fungi. Promising results were obtained, showing that synthesized compounds are, indeed, potential biologically active compounds with antimicrobial activity. Taking into account that pyridine derivatives also exhibit anticorrosion activity, the anticorrosive properties of thementioned compounds were also investigated in an aqueous solution–hydrocarbons (kerosene) medium. The obtained results demonstrated that the investigated compounds are excellent corrosion inhibitors in the aqueous solution–hydrocarbons (kerosene) medium.

Supplementary Information

Supplementary information is available in the website http://nopr.niscair.res.in/handle/123456789/58776.

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