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ORIGINAL ARTICLE

# Fatty Acids in Heterocyclic Synthesis. Part XIV: Synthesis of Surface Active Agents from Some Novel Class of Oxadiazole, Thiadiazole and Triazole Derivatives Having Microbiological Activities

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**Abstract** Reaction of stearic acid with semicarbazide in refluxing $POCl_3$ afforded 2-amino-5-heptadecyl 1,3,4-oxadiazole. Acylation of the amino group with acetic anhydride, ethyl chloroacetate and chloroacetic acid gave amide and β-amino acid derivatives. These compounds were cyclized to imidazo[2,1-*b*]oxadiazole derivatives by two different techniques. Treating the starting oxadiazole compound with $P_2S_5$, hydroxyl amine and hydrazine hydrate in benzene afforded thiadiazole and triazole derivatives. Unexpectedly, triazolo[3,4-*b*][1,3,4]oxadiazole derivative was obtained when 1,3,4-oxadiazole derivative was refluxed with hydrazine hydrate in ethanol. The biological activities of the synthesized compounds were screened in vitro against some gram positive and gram negative bacteria and fungi. Addition of quantitative amount of propylene oxide units (3, 5, 7 mol) to the synthesized compounds afforded new nonionic surfactants. The physico-chemical and surface properties of the novel synthesized surfactants such as surface and interfacial tension, cloud point, wetting time, emulsion stability, foam height, CMC, resistance to hydrolysis and their biodegradability were investigated. In addition, surface parameters including effectiveness ($\pi_{CMC}$), efficiency ($PC_{20}$), maximum surface excess ($\Gamma_{max}$) and ($A_{min}$) were examined.

**Keywords** Stearic acid · 2-Aminooxadiazole · Nonionic surfactant · Antimicrobial · Triazolo[3,4-*b*]oxadiazole · Imidazo[3,1-*b*]oxadiazole · Thiadiazole · Triazole · Surface properties

## Introduction

2-Amino oxadiazoles have a great importance in biological and industrial applications. They have bactericidal, fungicidal [1], herbicidal, and insecticidal activities [2]. In addition, they are employed as anti-inflammatory [3], analgesic [4], anticonvulsant, nervous system depressant [5], antiallergic [6] and antiviral drugs [7]. Conjugated systems of 2,5-disubstituted-[1,3,4]oxadiazoles often fluoresce, such a property makes them potentially useful as laser dyes, optical brighteners, scintillators, luminescent dyes and photosensitizing materials [8]. Having a long alkyl chain (hydrophobic part) attached to the oxadiazole nucleus increases their usefulness even further. Moreover, the introduction of a quantitative amount of hydrophilic part such as polyoxyethylene, or polyoxypropylene increases the solubility of 1,3,4-oxadiazoles in water and enhances the potential of their usage as nonionic surfactants. Generally, surfactants are one of the most important and widely used products in nearly every industrial sector. The growing and diverse applications of nonionic surfactants in therapy [9], industry [10], agriculture [11] and housing [12] prompted us to continue our research program on the utilization of fatty acids in heterocyclic synthesis, to synthesize novel nonionic surfactants [13–17]. Herein, we report the synthesis and some reactions of 2-amino-5-heptadecyl[1,3,4]oxadiazole (**1**) and the physico-chemical and surface properties of the novel synthesized surfactants.

**Electronic supplementary material** The online version of this article (doi:10.1007/s11743-013-1530-9) contains supplementary material, which is available to authorized users.

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## Experimental Protocols

### Materials

Stearic acid (Chemajet Chemical Company, 99 % GPR), semicarbazide hydrochloride (Winlab, 99 %), $POCl_3$ (Alpha Chemie, ≥98 %), 4-chlorobenzaldehyde [Fluka Chemika, ≥98 % (NT), piperidine (Merck Schuchardt, >98 % (GC)], acetic anhydride (Adwic, 98 %), ethyl chloroacetate (Loba Chemie, >98 %), chloroacetic acid [Aldrich, 99 % (T)], pyridine (LR) [SD Fine-Chem Limited, 99 % (GC)], glacial acetic acid (S D Fine-Chem Limited, 99 %), phosphorous pentasulfide (Sigma-Aldrich, 95 %), hydroxylamine hydrochloride (Winlab, 98 %), hydrazine hydrate (Loba Chemie, 80 %), benzene, toluene (Adwic), ethanol abs. (Adwic, 99 %), methanol (S D Fine-Chem Limited, 99 %). paraffin oil (Aldrich, dynamic viscosity; 110–230 mPa s, density; 0.827–0.890 g/mL at 20 °C).

### Structure Confirmation

The structural assignments of new compounds are based on their elemental analysis and spectral data (IR, $^1$H NMR, $^{13}$C NMR, and Mass spectra) (Full description of the obtained data are presented in the supplementary material section). All melting points are uncorrected and determined by the open capillary method using a Gallenkamp melting point apparatus.

IR spectra (KBr disk) of the synthesized compounds were recorded on FT/IR-BRUKER, Vector 22 (Germany), JASCO FT/IR-4100 (Japan), and JASCO FT/IR-460+ (Japan). $^1$H- and $^{13}$C-NMR spectra were recorded in deuterated chloroform ($CDCl_3$) or dimethyl sulfoxide (DMSO-$d_6$) as a solvent on a Varian Mercury VXR-300 spectrometer (200 MHz for $^1$H NMR and 75 MHz for $^{13}$C NMR) using TMS as internal reference. Chemical shifts are expressed in ppm. The mass spectra of compounds **1**, **7**, **11** and **12** were recorded on a Shimadzu GCMS-QP-1000EX mass spectrophotometer and those of **2–6** and **8–10** were recorded on a Shimadzu QP-2010 Plus mass spectrophotometer at 70 eV.

Homogeneity of all compounds synthesized was checked by TLC. All the synthesized compounds gave satisfactory elemental analyses. Surface active properties were carried out at the Chemistry Department, Faculty of Science, Benha University, Egypt. Antibacterial and antifungal activities were carried out in the Micro Analytical Center, Faculty of Science, Cairo University.

### Synthesis

*Synthesis of 2-amino-5-heptadecyl-1,3,4-oxadiazole* (**1**). A mixture of stearic acid (0.01 mol) and semicarbazide hydrochloride (0.01 mol) in (20 mL) $POCl_3$ was refluxed for 8 h. The reaction mixture was concentrated, cooled, and then poured onto ice while stirring. The produced solid was filtered off and recrystallized from ethanol. Compound **1** was obtained as a pale yellow powder in 77 % yield, mp 102–104 °C. Anal. Calc. (%) for $C_{19}H_{37}N_3O$: C; 70.54, H; 11.53, N; 12.99. Found: C; 70.23, H; 11.29, N; 12.81.

*Synthesis of (4-chloro-benzylidene)-(5-heptadecyl-[1,3,4]oxadiazol-2-yl)-amine* (**2**). A mixture of **1** (0.01 mol) and 4-chlorobenzaldehyde (0.01 mol) in ethanol (30 mL) in the presence of piperidine (0.5 mL) was refluxed for 6 h. The reaction mixture was concentrated, cooled and poured into ice-HCl. The obtained solid product was filtered off, dried and recrystallized from ethanol. Compound **2** was obtained as a white powder in 81 % yield, mp 136–138 °C. Anal. Calc. (%) for $C_{26}H_{40}ClN_3O$: C; 70.01, H; 9.04, N; 9.42, Cl; 7.95. Found: C; 70.13, H; 9.29, N; 9.61, Cl; 8.05.

*Synthesis of N-(5-heptadecyl-[1,3,4]oxadiazol-2-yl)-acetamide* (**3**). First, 0.01 mol of **1** was refluxed in 30 mL of acetic anhydride for 3 h. The reaction mixture was concentrated, poured into cold water (30 mL). The solid product obtained was filtered off, dried and recrystallized from acetic acid. Compound **3** was obtained as a deep brown powder in 75 % yield, mp 85–87 °C. Anal. Calc. (%) for $C_{21}H_{39}N_3O_2$: C; 69.00, H; 10.75, N; 11.49. Found: C; 69.13, H; 10.29, N; 11.61.

*Synthesis of 2-chloro-N-(5-heptadecyl-[1,3,4]oxadiazol-2-yl)-acetamide* (**4**). A mixture of **1** (0.01 mol) and ethyl chloroacetate (0.01 mol) in ethanol (30 mL) was refluxed for 8 h. The reaction mixture was concentrated and cooled. The solid product was filtered off, dried and recrystallized from ethanol. Compound **4** was obtained as a pale brown powder in 85 % yield, mp 132–134 °C. Anal. Calc. (%) for $C_{21}H_{38}ClN_3O_2$: C; 63.06, H; 9.58, N; 10.51, Cl; 8.86. Found: C; 63.23, H; 10.19, N; 10.62, Cl; 8.65.

*Synthesis of 2-[(5-heptadecyl-[1,3,4]oxadiazol-2-yl)amino]acetic acid* (**5**). A mixture of **1** (0.01 mol) and chloroacetic acid (0.01 mol) in benzene (30 mL) in the presence of piperidine (0.5 mL) was refluxed for 7 h. The reaction mixture was concentrated, cooled and poured into ice-HCl. The solid product obtained was filtered off, dried and recrystallized from benzene. Compound **5** was obtained as a pale gray powder in 71 % yield, mp 126–128 °C. Anal. Calc. (%) for $C_{21}H_{39}N_3O_3$: C; 66.14, H; 10.24, N; 11.02 Found: C; 66.45, H; 10.51, N; 10.69.

*Synthesis of 2-heptadecylimidazo[2,1-b][1,3,4]oxadiazol-6(5H)-one* (**6**). Initially, 0.01 mol of **4** was refluxed with benzene (30 mL) in the presence of pyridine (0.5 mL) for 5 h or subjected to fusion in an oil bath at 170 °C for 2 h. The reaction mixture was concentrated, cooled and poured into ice-HCl. The obtained solid product was filtered off, dried and recrystallized from ethanol. Compound

**6** was obtained as yellow powder in 70 % yield, mp 149–151 °C. Anal. Calc. (%) for $C_{21}H_{37}N_3O_2$: C; 69.38, H; 10.26, N; 11.56. Found: C; 69.55, H; 10.41, N; 11.68.

*Synthesis of 2-heptadecylimidazo[2,1-b][1,3,4]oxadiazol-5(6H)-one* (**7**). (0.01 mol) of **5** was refluxed in (30 mL) glacial acetic acid containing sodium acetate (0.01 mol) for 5 h or fused in an oil bath at 170 °C for 2 h. The reaction mixture was concentrated, cooled and poured into ice with stirring. The solid product obtained was filtered off, washed several times with water and recrystallized from ethanol. Compound **7** was obtained as a gray powder in 68 % yield, mp 161–163 °C. Anal. Calc. (%) for $C_{21}H_{37}N_3O_2$: C; 69.38, H; 10.26, N; 11.56. Found: C; 69.55, H; 10.41, N; 11.68.

*Synthesis of 2-amino-5-heptadecyl-1,3,4-thiadiazole* (**8**). A mixture of **1** (0.01 mol) and phosphorous pentasulfide (0.02 mol) was refluxed in (30 mL) dry xylene until the color changes into orange. The reaction mixture was filtered while hot and the filtrate was left to cool at room temperature. The obtained solid was filtered off, dried and recrystallized from benzene. Compound **8** was obtained as a yellow powder in 80 % yield, mp 110–112 °C. Anal. Calc. (%) for $C_{19}H_{37}N_3S$: C; 67.20, H; 10.98, N; 12.37, S; 9.44. Found: C; 66.91, H; 10.64, N; 12.08, S; 9.13.

*Synthesis of 3-amino-5-heptadecyl[1,2,4]triazol-4-ol* (**9**). A mixture of **1** (0.01 mol) and hydroxylamine hydrochloride (0.01 mol) was refluxed in (30 mL) pyridine for 4–5 h. The reaction mixture was cooled and poured into ice-HCl. The solid product obtained was filtered off, dried and recrystallized from benzene. Compound **9** was obtained as a greenish black powder in 69 % yield, mp 104–106 °C. Anal. Calc. (%) for $C_{19}H_{38}N_4O$: C; 67.41, H; 11.31, N; 16.55. Found: C; 67.53, H; 11.22, N; 16.78.

*Synthesis of 5-heptadecyl[1,2,4]triazole-3,4-diamine* (**10**). A mixture of **1** (0.01 mol) and hydrazine hydrate (0.01 mol) was refluxed in 30 mL of benzene for 6 h. The reaction mixture was concentrated and cooled. The solid was filtered off, dried and recrystallized from benzene. Compound **10** was obtained as a yellowish brown powder in 78 % yield, mp 94–96 °C. Anal. Calc. (%) for $C_{19}H_{39}N_5$: C; 67.61, H; 11.65, N; 20.75. Found: C; 67.54, H; 11.41, N; 20.58.

*Synthesis of 6-heptadecyl[1,2,4]triazolo[3,4-b][1,3,4]oxadiazol-3-amine (11) and ethyl-N-[amino(hydrazinylidene)methyl]heptadecylhydrazonoate* (**12**). A mixture of **1** (0.01 mol) and hydrazine hydrate (0.01 mol) was refluxed in 30 mL of ethanol for 5–6 h. Compound **11** was obtained directly on heating and separated, filtered off, dried and recrystallized from acetic acid. While the filtrate was concentrated, cooled then the solid **12** was filtered off, dried and recrystallized from ethanol. Compound **11** was obtained as a white powder in 69 % yield, mp 130–132 °C. Anal. Calc. (%) for $C_{20}H_{37}N_5O$: C; 66.08, H; 10.26, N; 19.26. Found: C; 66.14, H; 10.31, N; 19.31.

Compound **12** was obtained as a pale yellow powder in 73 % yield, mp 98–100 °C. Anal. Calc. (%) for $C_{21}H_{45}N_5O$: C; 65.75, H; 11.82, N; 18.26. Found: C; 65.58, H; 12.01, N; 18.39.

## Antimicrobial Activities

The antimicrobial susceptibility or resistance profile of the synthesized compounds was determined with the modified Kirby-Bauer disc diffusion technique [18–21], using Mueller–Hinton agar.

One hundred microliters of the test bacteria/fungi were grown in 10 mL of fresh media until they reached a count of approximately 108 cells/mL for bacteria and 105 cells/mL for fungi. The microbial suspension (100 µl) was spread onto agar plates that are relevant to the broth in which they are maintained. Standard discs of Tetracycline (Antibacterial agent), Amphotericin B (Antifungal agent) were used as positive control for antimicrobial activity, while filter discs impregnated with 10 µl of solvent (distilled water, chloroform, DMSO) were used as a negative control. Blank paper discs (Schleicher and Schuell, Spain) with a diameter of 8.0 mm were impregnated with 10 µl of the tested concentration.

When the filter paper disc impregnated with the tested compound (of known concentration) was placed on agar, the compound diffused from the disc into the agar in the area around the disc. The solubility of the tested compound and its molecular size determine the size of the area of its infiltration around the disc. An organism that is susceptible to the tested compound will not grow in the area around the disc. The size of this inhibition zone is used as a measure of the antimicrobial activity "A" of a tested compound at its minimum inhibitory concentration (MIC). The observed data on the antimicrobial activity of the compounds are given in Table 1.

## Preparation of Nonionic Surfactants from the Synthesized Heterocyclic Compounds

### *Propoxylation (hydroxylation)*

Following Morgos procedure [22], 0.5 wt% KOH solution containing 0.01 mol of the synthesized compound was stirred and heated to 70 °C while passing a slow stream of nitrogen through the system to flush out oxygen. The nitrogen stream was stopped and propylene oxide was added drop-wise with continuous stirring and heating under an efficient reflux system to retain the propylene oxide. The reaction was conducted for different intervals of time ranging from 1–10 h. The apparatus was then filled with

**Table 1** Antimicrobial activity of compounds **1–12**

| Sample | Inhibition zone diameter (mm/mg sample) | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| | *Escherichia coli* $G^-$ | | *Staphylococcus aureus* $G^+$ | | *Aspergillus flavus* Fungus | | *Candida albicans* Fungus | |
| | MIC | A | MIC | A | MIC | A | MIC | A |
| Control: DMSO | – | 0.0 | – | 0.0 | – | 0.0 | – | 0.0 |
| Positive reference | | | | | | | | |
| *Tetracycline* | 200 | 31 | 200 | 30 | – | – | – | – |
| *Amphotericin B* | – | – | – | – | 200 | 16 | 200 | 19 |
| **1** | 100 | 14 | 200 | 13 | 400 | 0.0 | 400 | 0.0 |
| **2** | 200 | 11 | 200 | 11 | 400 | 0.0 | 400 | 0.0 |
| **3** | 200 | 10 | 100 | 11 | 400 | 0.0 | 400 | 0.0 |
| **4** | 400 | 12 | 200 | 11 | 400 | 0.0 | 400 | 0.0 |
| **5** | 400 | 11 | 100 | 10 | 400 | 0.0 | 400 | 0.0 |
| **6** | 400 | 15 | 100 | 14 | 400 | 11 | 400 | 0.0 |
| **7** | 400 | 14 | 200 | 13 | 400 | 12 | 400 | 0.0 |
| **8** | 100 | 14 | 200 | 15 | 400 | 0.0 | 400 | 0.0 |
| **9** | 100 | 13 | 400 | 13 | 400 | 0.0 | 400 | 0.0 |
| **10** | 100 | 18 | 200 | 15 | 400 | 0.0 | 400 | 12 |
| **11** | 100 | 16 | 200 | 14 | 400 | 13 | 400 | 11 |
| **12** | 200 | 12 | 100 | 11 | 400 | 0.0 | 400 | 0.0 |

A = 0.0, Not active; A < 7 mm, slightly active; A > 15 mm, moderately active; A > 20 mm, highly active

*MIC* minimum inhibitory, *A* antimicrobial activity of tested compounds; concentration

nitrogen and cooled. The reaction vessel was weighed. The amount of reacted propylene oxide and the average degree of propoxylation were determined from the increment in the mass of the reaction mixture [23]. The selected average numbers of moles, *n*, are 3, 5 and 7.

## Surface Active Properties of Surfactants

### *Surface and Interfacial Tensions*

Surface and interfacial tension measurements on **I(a–c)–IX(a–c)** were carried out according to Findlay [24] with a Krüss tensiometer [25] (Krüss GmbH, Hamburg, Instrument Nr. K6) for different concentrations of the synthesized surfactants (0.05–$10^{-6}$ mol/L), using a platinum-iridium ring at constant temperature (25 ± 1 °C). Paraffin oil was used for the interfacial tension measurements. The tensiometer was calibrated using the method described in ASTM Designation: D1331-01 [26].

### *Cloud Point*

The cloud point is a measure of the inverse solubility of a nonionic surface active agent. In a temperature-controlled bath, a 1-wt% solution of the tested compound was gradually heated until the clear or nearly clear solution became definitely turbid [27]. The temperature was then recorded and the solution was allowed to cool down until it became clear again. The process was repeated to check the reproducibility of the recorded temperature.

### *Wetting Time*

Wetting time was measured by immersing a cotton skein (1 g) in a 0.1 wt% solution of the prepared surfactants in distilled water at 25 °C according to the Draves technique [28]. The sinking time was measured in seconds.

### *Foaming Properties*

Foam height was measured by the Ross Miles method [29]. In this procedure a given surfactant solution was allowed to fall from a set height into the same surfactant solution in a volumetric cylinder, hence creating foam. The height of the foam was visually assessed.

### *Emulsion Stability*

The emulsifying property of the prepared surfactants was determined as follows: In a 100-mL graduated stoppered tube; an aqueous solution of the surfactant (10 mL, 20 mol) was mixed with light paraffin oil (6 mL). The mixture was shaken vigorously by magnetic stirring [Thermo scientific Cimarec™ stirring hot plate, model

no: sp131320-30, estimated stirring speed (1,100 rpm)] for 2 min at 25 °C. The tube was placed upright and the separation of the formed emulsion was observed. The time taken for the separation of (9 mL) of the aqueous layer indicates the emulsion stability of the surfactant [30].

*Critical Micelle Concentration (CMC) Measurements*

The critical micelle concentration (CMC) is the minimum concentration at which surfactants molecules begin to form micelles [31]. CMC values were obtained through a conventional plot of the surface tension versus the logarithm of concentration of surfactant. The CMC concentration corresponds to the point where the surfactant first shows the lowest surface tension, and after which the surface tension remains nearly constant.

*Effectiveness ($\pi_{CMC}$)*

The effectiveness of a certain surfactant $\pi_{CMC}$ is expressed in terms of the decrease in the surface tension that is induced by this surfactant at the critical micelle concentration [32]. It is calculated from the difference between the surface tension of pure water ($\gamma_0$) and the surface tension of the surfactant solution at the critical micelle concentration ($\gamma_{CMC}$), Eq. (1).

$$\pi_{CMC} = \gamma_0 - \gamma_{CMC} \quad (1)$$

*Efficiency ($PC_{20}$)*

Efficiency of a surfactant ($PC_{20}$) is defined by the values of the negative logarithm of the bulk concentration necessary to reduce surface tension by 20 mN/m [33]. It can be calculated from the following equation, Eq. (2).

$$PC_{20} = \frac{\gamma - 20 - \gamma_{CMC}}{2.303nRT} - \log C_{CMC} \quad (2)$$

where $R$ universal gas constant $8.31 \times 10^7$ ergs $mol^{-1}$ $K^{-1}$. $T$ absolute temperature K.

*Maximum Surface Excess $\Gamma_{max}$*

The values of the maximum surface excess $\Gamma_{max}$—expressed in $mol/cm^2$ were calculated from surface or interfacial data by the use of Gibbs equation [34], Eq. (3):

$$\Gamma_{max} = \frac{-1}{2.303} RT \left( \frac{\delta\gamma}{\delta \log C} \right)_T \quad (3)$$

where $\delta\gamma$ surface pressure in mN/m. $C$ surfactant concentration. $(\delta\gamma/\delta \log C)_T$ is the slope of a plot of surface tension versus concentration curves below CMC at constant temperature.

*Minimum Surface Area ($A_{min}$)*

Knowing $\Gamma_{max}$, it is easy to calculate the effective area occupied by each surfactant molecule adsorbed at the air/water interface at surface saturation [35, 36]. The average area $A_{min}$ (in $Å^2$/mol) is given by Eq. (4):

$$A_{min} = {}^{10^{16}}/_{\Gamma_{max} N} \quad (4)$$

where $N$ Avogadro's number $6.023 \times 10^{23}$.

*Resistance to Hydrolysis*

The resistance of a certain surfactant towards acid and base hydrolysis was established by measuring the surface tension of that surfactant in acidic and alkaline media. Thus, the surface tension of a 0.1 % solution of the surfactant in 5 % sulfuric acid or in 1 % sodium hydroxide was measured at room temperature after boiling for 30 and 60 min.

*Biodegradability of the Synthesized Surfactants*

The biodegradation tests of the synthesized nonionic surfactants were performed according to the River Water Die-Away method [37]. The river water for testing was sampled from the River Nile. In this test, a stirred solution containing the tested surfactant (1,000 ppm) was incubated at 25 °C. Samples were withdrawn daily, filtered using Whatman filter paper and the surface tension was measured using a Du-Nouy tensiometer (Kruss type K6). The process was repeated for 7 days. The biodegradation percentage $D\%$ was calculated in terms of the measured surface tension according to Eq. (5):

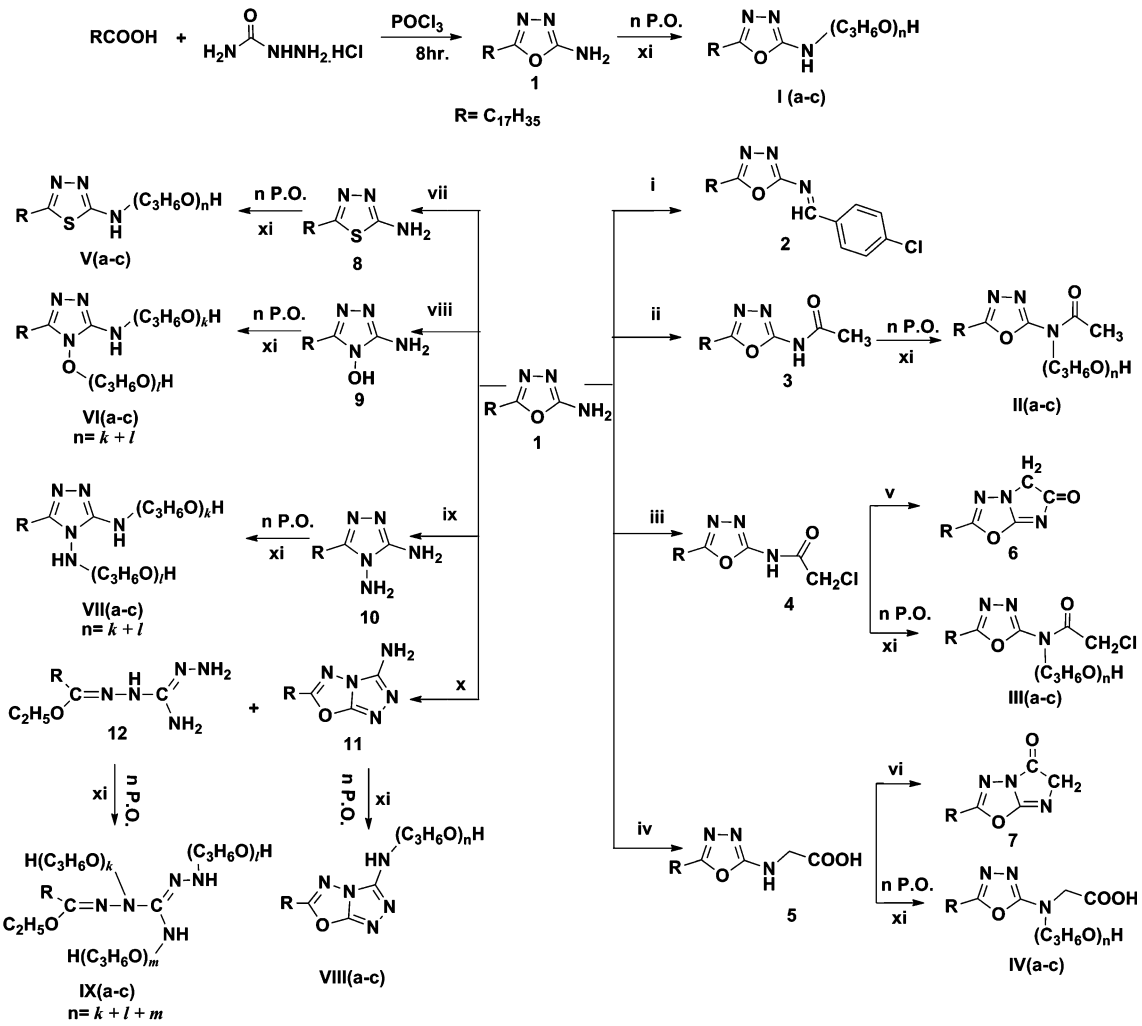
$$D = [(\gamma_t - \gamma_0)/(\gamma_{bt} - \gamma_0)] \times 100 \quad (5)$$

where $\gamma_t$ surface tension at time $t$. $\gamma_0$ surface tension at time zero (initial surface tension). $\gamma_{bt}$ surface tension of the blank experiment at time $t$.

## Results and discussion

In continuation of our research program on the utilization of fatty acids in the synthesis of heterocyclic compounds as precursors for novel nonionic surfactant [13–17], herein we report the synthesis and some reactions of 2-amino-5-heptadecyl[1,3,4]oxadiazole (**1**) (Scheme 1). Thus, the reaction of stearic acid with semicarbazide hydrochloride in refluxing $POCl_3$ afforded **1** in good yield. Formation of **1** was confirmed by spectroscopic tools, for instance, the mass spectra showed [$\dot{M}^+$] at 323 (1.0 %).

Condensation of compound **1** with *p*-chlorobenzaldehyde produced a Schiff's base, namely, (4-chloro-benzylidene)-(5-heptadecyl-[1,3,4]oxadiazol-2-yl)-amine (**2**), while



**Scheme 1** Synthetic routes of compounds **1–12** and surfactants **I–IX** (**i**) *p*-Chlorobenzaldehyde, ethanol, piperidine, reflux 6 h; (**ii**) acetic anhydride, reflux 3 h; (**iii**) Cl–$CH_2$COOEt, EtOH, reflux 8 h; (**iv**) Cl–$CH_2$COOH, benzene, piperidine, reflux 7 h; (**v**) benzene, pyridine, reflux 5 h/or fusion in oil-bath for 2 h; (**vi**) AcOH, AcONa, reflux 5 h/ or fusion for 2 h in oil-bath; (**vii**) $P_2S_5$, dry xylene, reflux till orange color; (**viii**) $NH_2$OH.HCl, pyridine, reflux 4–5 h.; (**ix**) $N_2H_4{\cdot}H_2O$, benzene, reflux 6 h; (**x**) $N_2H_4{\cdot}H_2O$, EtOH, reflux 5–6 h; (**xi**) $n = 3$, 5 and 7 mol of propylene oxide (P.O.)

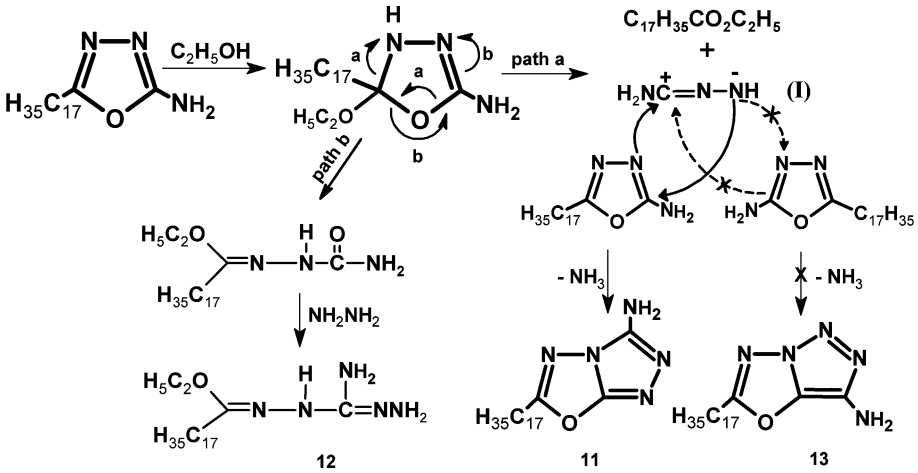
acetylation of compound **1** with $Ac_2O$ produced *N*-(5-heptadecyl[1,3,4]oxadiazol-2-yl)acetamide **(3)**.

Reaction of 2-amino oxadiazole **1** with ethyl chloroacetate in refluxing ethanol and with chloroacetic acid in benzene in the presence of catalytic amount of piperidine, produced 2-chloro-*N*-(5-heptadecyl[1,3,4]oxadiazol-2-yl)acetamide **(4)** and 2-[(5-heptadecy[1,3,4]-oxadiazol-2-yl) amino]acetic acid **(5)**, respectively.

Furthermore, in order to increase the utility of oxadiazoles, compounds **4** and **5** were subjected to cyclization. Thus, cyclization of compound **4** either by fusion or refluxing in benzene in the presence of pyridine produced 2-heptadecylimidazo[2,1-*b*][1,3,4]oxadiazol-6(5*H*)-one **(6)**; the formation of which was confirmed by spectroscopic analysis. IR of compound **6** lacked any $\nu_{NH}$ but showed $\nu_{C=O}$ of α-β unsaturated five-membered ketone at 1,674 $cm^{-1}$. The mass spectrum showed $[\dot{M}^+]$ and $[\dot{M}^+]+1$ at 363 (0.68 %) and 364 (0.81 %), respectively.

Cyclization of compound **5** using sodium acetate in acetic acid afforded 2-heptadecyl- imidazo[2,1-*b*][1,3,4]oxadiazol-5(6*H*)-one **(7)**. The formation of **7** was evident from its IR which lacked any bands for the carboxy hydroxyl group, and showed the expected $\nu_{C=O}$ of unconjugated cyclic five membered ketone at 1,681 $cm^{-1}$. $^1$H NMR showed singlet band at 2.88 ppm for cyclic $CH_2$ moiety which supported the proposed structure.

Substitution of the oxygen atom of oxadiazoles by a sulfur or nitrogen atom represents a vital route to obtain thiadiazole or triazole derivatives, respectively. Thus, when oxadiazole **1** was allowed to react with $P_2S_5$ in refluxing xylene, 2-amino-5-heptadecyl[1,3,4]-thiadiazole **(8)** was obtained.




**Scheme 2** Proposed mechanism for the formation of compounds **11** and **12**

The synthesis of compound **8** was previously achieved by the reaction of thiosemicarbazide and stearic acid [38].

On the other hand, reaction of **1** with hydroxylamine hydrochloride in pyridine afforded 3-amino-5-heptadecyl[1,2,4]triazol-4-ol (**9**). Similarly, oxadiazole **1** reacted with hydrazine hydrate in refluxing benzene to give 5-heptadecyl [1,2,4]triazole 3,4-diamine **(10)**.

Contrary to what was expected, carrying out the reaction in boiling ethanol afforded two different compounds, none of them being the expected triazole **10**. These compounds were identified as 6-heptadecyl[1,2,4]triazolo[3,4-*b*][1,3,4]oxadiazol-3-amine (**11**) and ethyl-*N*-[amino(hydrazinylidene)methyl]heptadecylhydrazonoate (**12**). The mechanism proposed to account for the formation of **11** and **12** involved an initial nucleophilic attack of ethanol on the oxadiazole nucleus followed either by cycloelimination [path a] with the subsequent 1,3-dipolar cycloaddition of intermediate (**I**) to **1** leading to the formation of the thermodynamically more stable triazole **11** rather than 5-heptadecyl[1,2,3]triazolo[5,1-*b*][1,3,4]oxadiazol-3-amine (**13**); or by ring opening [path b] with the subsequent reaction with hydrazine to produce (**12**) (Scheme 2). The formation of the isomeric triazole (**13**) is ruled out since its formation necessitates 1,3-dipolar cycloaddition of intermediate (**I**) with inverse electron demand (Scheme 2), in addition, ab initio calculations at the RHF/6-31G level indicated that the triazole **11** is more stable than **13** by 22.24 kcal/mol. The structure of both compounds was confirmed by spectroscopic analysis. Similar heterolytic addition of low molecular weight alcohols to the C=N of oxadiazole has been reported for the photochemical reaction of 2-phenyl- and 2,5-diphenyl-1,3,4-oxadiazoles [39, 40].

## Antimicrobial Activities of the Synthesized Oxadiazole Derivatives

All the synthesized compounds (**1–12**) were screened in vitro (using a modified Kirby-Bauer disc diffusion method [18–21] against Gram-negative bacteria, namely, *Escherichia coli*, Gram-positive bacteria *Staphylococcus aureus* and fungi namely, *Aspergillus flavus* and *Candida albicans*. Tetracycline and Amphotericin B were taken as positive references for antibacterial and antifungal agents, respectively. The antimicrobial activity A of a tested compound is determined at its minimum inhibitory concentration (MIC), i.e. at the lowest concentration of the compound that completely inhibited visible growth of a specific microorganism.

As outlined in Table 1, the synthesized compounds show varying degrees of inhibition against the tested microorganisms. Thus, while 5-heptadecyl-[1, 3, 4]oxadiazole derivatives **(1–5)**, 2-amino-5-heptadecyl[1,3,4]-thiadiazole (**8**), 5-heptadecyl-[1,3,4]triazole derivative (**9**), and hydrazinylidene hydrazonoate derivative **(12)** are inactive toward the tested fungi, they have exhibited moderate activity against both bacteria strains. On the other hand, imidazo[2, 1-*b*][1,3,4]oxadiazolone derivatives (**6**,**7**) exhibit moderate to high activity towards the tested bacteria strains and exhibit good antifungal activity against *Aspergillus flavus*, while, 5-heptadecyl [1,2,4]triazole 3, 4-diamine **(10)** reveals good activity toward both bacteria strains and exhibits moderate antifungal activity against *Candida albicans*. Triazolo[3,4-*b*][1,3,4]oxadiazole **(11)** is considered to be the most active compound in this series since it shows good to very good activity against both bacterial and fungal strains. These results are in agreement with previously reported results for oxadiazole, oxathiazole and triazoles derivatives [41–44].

## Nonionic Surfactants from Some Synthesized Compounds

Propoxylation of some of the new compounds (**1**, **3**, **4**, **5** and **8–12**) with various quantities of propylene oxide (3, 5, and 7 mol) produced nonionic surfactants **I(a–c)- IX(a–c)**, the

structure of which was confirmed via IR and $^1$H-NMR spectra. Thus, in addition to the original bands reported for these compounds, IR spectrum showed a broad band in the region (3,500–2,500) $cm^{-1}$ (υOH) and two other bands in the region (1,100–1,000) and (950–900) $cm^{-1}$ for (υC–O–C ether linkage of polypropoxy chain). The $^1$H-NMR spectrum showed the protons of the propyleneoxy groups which appear as broad multiple signals in the region (3.2–3.7) ppm. The physical properties of these compounds are shown in Table 2.

## Surface Active Properties

The surface active properties of the prepared propoxylated compounds **I(a–c)** to **IX(a–c)** were measured in a neutral medium. The data obtained are outlined in Table 3a, b.

### *Surface and Interfacial Tensions*

Surfactants are used in a large number of applications due to their ability to alter the energy relationships at interfaces and to lower the surface and interfacial tension [45]. As surfactant molecules dissolve in water, they orientate themselves in-between the water molecules and weaken the hydrogen bond between them. This in turn decreases the holding forces and lowers the surface and interfacial tension. The extent by which the surfactant decreases the surface tension depends on two competing forces. These are the repulsion forces between water molecules and the hydrophobic part of the surfactant; and the attraction forces between water molecules and the hydrophilic part of the surfactant molecules. In the case at hand, the hydrophobic part (heptadecyl side chain) is constant, while the hydrophilic part changes as the number of the propylene oxide units changes. Consequently, for a certain molecule, at a certain concentration, while the abovementioned repulsive force is unchanged, increasing the number of propylene oxide units increases the attractive forces. As a consequence and in accordance with the previously reported results [46], the surface and interfacial tensions of the solution increases by increasing the number of propylene oxide units (*n*) included in the molecule, Table 3a. In addition, comparing structurally related surfactants **I(a–c)** and **V(a–c)–VI I(a–c)** indicated that, at a certain (*n*) thiadiazole derivative **V(a–c)** is slightly more effective in decreasing the surface tension than oxadiazole **I(a–c)** and triazole derivatives **VII(a–c)** and **VI I(a–c)**. Within the oxadiazole derivatives **I(a–c)–IV(a–c)**, surfactants **III(a–c)** induce the highest reduction in surface and interfacial tensions.

**Table 2** Physicochemical properties of the synthesized surfactants

| Compd. | M. F. | M.wt | Color | Shape |
|---|---|---|---|---|
| **Ia** | $C_{28}H_{55}N_3O_4$ | 497 | Yellow | Semi-solid |
| **Ib** | $C_{34}H_{67}N_3O_6$ | 613 | Yellow | Semi-solid |
| **Ic** | $C_{40}H_{79}N_3O_8$ | 729 | Yellow | Semi-solid |
| **IIa** | $C_{30}H_{57}N_3O_5$ | 539 | Black | Powder |
| **IIb** | $C_{36}H_{69}N_3O_7$ | 655 | Black | Powder |
| **IIc** | $C_{42}H_{81}N_3O_9$ | 771 | Black | Powder |
| **IIIa** | $C_{30}H_{56}N_3O_5Cl$ | 573 | Brown | Semi-solid |
| **IIIb** | $C_{36}H_{68}N_3O_7Cl$ | 689 | Brown | Semi-solid |
| **IIIc** | $C_{42}H_{80}N_3O_9Cl$ | 805 | Brown | Semi-solid |
| **IVa** | $C_{30}H_{57}N_3O_6$ | 555 | Dark-gray | Semi-solid |
| **IVb** | $C_{36}H_{69}N_3O_8$ | 671 | Dark-gray | Semi-solid |
| **IVc** | $C_{42}H_{81}N_3O_{10}$ | 787 | Dark-gray | Semi-solid |
| **Va** | $C_{28}H_{55}N_3O_3S$ | 513 | Pale-yellow | Powder |
| **Vb** | $C_{34}H_{67}N_3O_5S$ | 629 | Pale-yellow | Powder |
| **Vc** | $C_{40}H_{79}N_3O_7S$ | 745 | Pale-yellow | Powder |
| **VIa** | $C_{28}H_{56}N_4O_4$ | 512 | Dark-green | Semi-solid |
| **VIb** | $C_{34}H_{68}N_4O_6$ | 628 | Dark-green | Semi-solid |
| **VIc** | $C_{40}H_{80}N_4O_8$ | 744 | Dark-green | Semi-solid |
| **VIIa** | $C_{28}H_{57}N_5O_3$ | 511 | Brown | Semi-solid |
| **VIIb** | $C_{34}H_{69}N_5O_5$ | 627 | Brown | Semi-solid |
| **VIIc** | $C_{40}H_{81}N_5O_7$ | 743 | Brown | Semi-solid |
| **VIIIa** | $C_{29}H_{55}N_5O_4$ | 537 | White | Powder |
| **VIIIb** | $C_{35}H_{67}N_5O_6$ | 653 | White | Powder |
| **VIIIc** | $C_{41}H_{79}N_5O_8$ | 769 | White | Powder |
| **IXa** | $C_{30}H_{63}N_5O_4$ | 557 | Yellow | Semi-solid |
| **IXb** | $C_{36}H_{75}N_5O_6$ | 673 | Yellow | Semi-solid |
| **IXc** | $C_{42}H_{87}N_5O_8$ | 789 | Yellow | Semi-solid |

### *Cloud Point*

For nonionic surfactants, a common and characteristic observation is that they exhibit a reverse solubility versus temperature behavior in water, consequently their solutions tend to become visibly turbid at a well-defined temperature. This is known as the cloud point, above which the surfactant solution phase separates into two phases. The cloud point is a critical factor in the performance of nonionic surfactants; generally, nonionic surfactants show optimal effectiveness when used near or below their cloud point. In addition, knowing the cloud point helps us to determine the storage stability since storing at temperatures significantly higher than the cloud point may result in phase separation and instability. The cloud point depends on the chemical structure [47, 48]. For a given hydrophobic group the cloud point is found to increase with increasing the length of the hydrophilic moiety [49, 50]. As outlined in Table 3a, the cloud point for the synthesized surfactants increases by increasing the number of propylene oxide groups.

### *Wetting Time*

The degree of wetting is the resultant of two competing forces. These are, adhesive forces between a liquid and

**Table 3** Surface properties of some synthesized surfactants

| Compd. | No. of moles[a] | Surface tension (mN/m) 0.1 wt% | Interfacial tension (mN/m) 0.1 wt% | Cloud point (°C) 1.0 wt% | Wetting time (s) 0.1 wt% | Foam height (mm) 1.0 wt% | Emulsion stability (min) 20 mol |
|---|---|---|---|---|---|---|---|
| (a) | | | | | | | |
| **I(a–c)** | 3 | 33 | 10 | 86 | 52 | 70 | 45 |
| | 5 | 35 | 13 | 93 | 47 | 80 | 43 |
| | 7 | 38 | 15 | >100 | 42 | 100 | 40 |
| **II(a–c)** | 3 | 34 | 9 | 82 | 50 | 50 | 44 |
| | 5 | 36 | 12 | 98 | 47 | 70 | 42 |
| | 7 | 39 | 13 | >100 | 48 | 90 | 38 |
| **III(a–c)** | 3 | 29 | 8 | 81 | 44 | 90 | 49 |
| | 5 | 30 | 10 | 95 | 39 | 100 | 46 |
| | 7 | 33 | 13 | >100 | 38 | 120 | 42 |
| **IV(a–c)** | 3 | 31 | 11 | 86 | 53 | 100 | 52 |
| | 5 | 33 | 14 | 94 | 48 | 120 | 49 |
| | 7 | 36 | 16 | >100 | 45 | 150 | 44 |
| **V(a–c)** | 3 | 31 | 10 | 85 | 50 | 60 | 44 |
| | 5 | 32 | 12 | 90 | 46 | 80 | 42 |
| | 7 | 34 | 14 | >100 | 40 | 100 | 38 |
| **VI(a–c)** | 3 | 34 | 12 | 86 | 54 | 90 | 42 |
| | 5 | 36 | 14 | 95 | 50 | 110 | 38 |
| | 7 | 37 | 16 | >100 | 46 | 120 | 36 |
| **VII(a–c)** | 3 | 37 | 13 | 89 | 52 | 90 | 55 |
| | 5 | 41 | 15 | 97 | 48 | 100 | 52 |
| | 7 | 43 | 16 | >100 | 45 | 120 | 46 |
| **VIII(a–c)** | 3 | 30 | 11 | 88 | 50 | 100 | 52 |
| | 5 | 31 | 13 | 96 | 48 | 120 | 49 |
| | 7 | 33 | 15 | >100 | 46 | 150 | 44 |
| **IX(a–c)** | 3 | 33 | 10 | 82 | 43 | 90 | 46 |
| | 5 | 34 | 12 | 91 | 40 | 110 | 43 |
| | 7 | 36 | 13 | >100 | 38 | 120 | 40 |

| Compd. | No. of moles[a] | CMC (mmol/L) | $\gamma_{CMC}$ (mN/m) | $\pi_{CMC}$ mN/m | $PC_{20}$ (mmol/L) | $\Gamma_{max}$ (mol/cm$^2$) | $A_{min}$ (Å$^2$/mol) |
|---|---|---|---|---|---|---|---|
| (b) | | | | | | | |
| **I(a–c)** | 3 | 5.0 | 34 | 38 | 2.30 | 0.99 | 1.66 |
| | 5 | 7.8 | 37 | 35 | 2.11 | 1.89 | 0.88 |
| | 7 | 10.0 | 39 | 33 | 2.00 | 2.27 | 0.73 |
| **II(a–c)** | 3 | 10.0 | 34.5 | 37.5 | 2.00 | 0.95 | 1.73 |
| | 5 | 12.0 | 37.5 | 34.5 | 1.92 | 1.82 | 0.91 |
| | 7 | 19.9 | 39 | 33 | 1.70 | 2.19 | 0.75 |
| **III(a–c)** | 3 | 3.1 | 29 | 43 | 2.51 | 0.84 | 1.97 |
| | 5 | 3.9 | 31 | 41 | 2.41 | 1.62 | 1.02 |
| | 7 | 5.4 | 34 | 38 | 2.27 | 1.97 | 0.84 |
| **IV(a–c)** | 3 | 0.64 | 32 | 40 | 3.19 | 0.98 | 1.65 |
| | 5 | 0.95 | 35.5 | 36.5 | 3.02 | 1.88 | 0.87 |
| | 7 | 1.9 | 38 | 34 | 2.72 | 2.26 | 0.72 |
| **V(a–c)** | 3 | 4.0 | 31 | 41 | 2.40 | 0.80 | 2.06 |
| | 5 | 5.6 | 33 | 39 | 2.25 | 1.55 | 1.07 |
| | 7 | 9.0 | 35 | 37 | 2.05 | 1.89 | 0.87 |
| **VI(a–c)** | 3 | 2.0 | 35 | 37 | 2.70 | 0.97 | 1.70 |
| | 5 | 4.5 | 36.5 | 35.5 | 2.35 | 1.85 | 0.89 |
| | 7 | 11.0 | 39 | 33 | 1.96 | 2.23 | 0.74 |
| **VII(a–c)** | 3 | 14.0 | 38 | 34 | 1.85 | 1.14 | 1.44 |
| | 5 | 59.0 | 42 | 30 | 1.23 | 2.15 | 0.77 |
| | 7 | 81.0 | 45 | 27 | 1.09 | 2.57 | 0.64 |

**Table 3** continued

| Compd. | No. of moles[a] | CMC (mmol/L) | $\gamma_{CMC}$ (mN/m) | $\pi_{CMC}$ mN/m | $PC_{20}$ (mmol/L) | $\Gamma_{max}$ (mol/cm$^2$) | $A_{min}$ (Å$^2$/mol) |
|---|---|---|---|---|---|---|---|
| **VIII(a–c)** | 3 | 3.8 | 30 | 42 | 2.42 | 0.79 | 2.05 |
| | 5 | 5.1 | 33 | 39 | 2.29 | 1.59 | 1.09 |
| | 7 | 6.0 | 34 | 38 | 2.22 | 1.89 | 0.87 |
| **IX(a–c)** | 3 | 5.3 | 34 | 38 | 2.28 | 0.98 | 1.68 |
| | 5 | 7.7 | 35 | 37 | 2.11 | 1.87 | 0.88 |
| | 7 | 10.7 | 38 | 34 | 1.97 | 2.25 | 0.73 |

[a] Number of propylene oxide units

solid that causes a liquid drop to spread across the surface; and cohesive forces within the liquid which causes the drop to ball up and avoid contact with the surface. Addition of surfactants to water lowers the surface and interfacial tension; this in turn lowers the contact angle between the liquid–vapor interface and the solid–liquid interface; resulting in more surface wetting. Consequently, surfactants are commonly used as wetting agents. In the present work, the efficiency of the synthesized surfactants as wetting agents was measured in terms of wetting time

**Table 4** Resistance of the synthesized surfactants towards acidic and alkaline hydrolysis

| Compd | Surface tension (mN/m) 0.1 wt | Surface tension of 0.1 % surfactant (stability to hydrolysis) | | | | | |
|---|---|---|---|---|---|---|---|
| | | $H_2SO_4$ (5 %) 25 °C | After boiling (5 %)$H_2SO_4$ | | NaOH (1 %) 25 °C | After boiling (1 %NaOH) | |
| | | | 30 min | 60 min | | 30 min | 60 min |
| **Ia** | 33 | 34 | 34 | 36 | 33 | 34 | 34 |
| **Ib** | 35 | 36 | 37 | 40 | 36 | 36 | 37 |
| **Ic** | 38 | 38 | 39 | 40 | 38 | 38 | 38 |
| **IIa** | 34 | 35 | 36 | 38 | 34 | 35 | 35 |
| **IIb** | 36 | 37 | 37 | 38 | 37 | 37 | 37 |
| **IIc** | 39 | 39 | 39 | 42 | 39 | 40 | 40 |
| **IIIa** | 29 | 30 | 31 | 34 | 29 | 30 | 30 |
| **IIIb** | 30 | 31 | 33 | 34 | 30 | 30 | 31 |
| **IIIc** | 33 | 34 | 34 | 36 | 33 | 33 | 34 |
| **IVa** | 31 | 32 | 33 | 34 | 31 | 31 | 31 |
| **IVb** | 33 | 35 | 36 | 36 | 33 | 34 | 34 |
| **IVc** | 36 | 37 | 38 | 40 | 37 | 37 | 38 |
| **Va** | 31 | 33 | 33 | 36 | 32 | 32 | 33 |
| **Vb** | 32 | 34 | 34 | 35 | 32 | 33 | 33 |
| **Vc** | 34 | 36 | 36 | 38 | 34 | 35 | 35 |
| **VIa** | 34 | 35 | 35 | 37 | 34 | 34 | 35 |
| **VIb** | 36 | 36 | 37 | 40 | 37 | 37 | 37 |
| **VIc** | 37 | 39 | 40 | 41 | 38 | 38 | 39 |
| **VIIa** | 37 | 39 | 40 | 43 | 37 | 38 | 38 |
| **VIIb** | 41 | 41 | 43 | 44 | 41 | 41 | 42 |
| **VIIc** | 43 | 44 | 46 | 46 | 43 | 44 | 44 |
| **VIIIa** | 30 | 31 | 33 | 34 | 30 | 30 | 31 |
| **VIIIb** | 31 | 32 | 32 | 34 | 32 | 33 | 33 |
| **VIIIc** | 33 | 33 | 34 | 37 | 34 | 35 | 35 |
| **IXa** | 33 | 34 | 36 | 37 | 33 | 33 | 34 |
| **IXb** | 34 | 35 | 36 | 39 | 34 | 35 | 35 |
| **IXc** | 36 | 38 | 41 | 42 | 37 | 37 | 37 |

according to Draves technique [28], which measures the ability of a surfactant solution to displace air from a weighted skein of cotton by spreading wetting. Shorter wetting times indicate more efficient wetting. Surfactants **I(a–c)** to **IX(a–c)** demonstrate varying wetting abilities depending on the number of propylene oxide units ($n$) (Table 3a). For a given surfactant, increasing ($n$) increases the adhesive forces relative to the cohesive forces [51] with the concomitant decrease of wetting time. Surfactants **IIIc** and **IXc** exhibited the shortest sinking time, consequently, are the most efficient wetting agents among the studied group. This may be attributed to the increase in the adhesive forces due to the presence of chlorine atom and ethoxy group in **III** and **IX**, respectively.

*Foaming Properties*

Foam consists of gas covered with thin liquid film. It is thermodynamically unstable and tends to collapse to liquid which is the lowest energy state. In solution, the presence of a surfactant lowers the surface tension and eases foam generation with simultaneous adsorption of the surfactant molecules onto the interface between gas and liquid. The adsorption of surfactant molecules at the foam walls opposes their collapse. The foamability of the synthesized surfactant was examined using the Ross Miles method [29]. As indicated in Table 3a, and in agreement with previous reports [51–53], the foam height of the synthesized surfactants increases by increasing the propylene oxide units per molecule of surfactant. These results suggest that increasing the adhesive forces—brought upon by increasing ($n$)- draws more surfactant to the interface which in turn enhances the formation of foam.

*Emulsion Stability*

Emulsification is an important property of surfactants that broadens their applications. For instance, tiny fragments of oil suspended in pure water will spontaneously assemble themselves into much larger masses. In the presence of an appropriate surfactant, the interfacial tension between the two immiscible liquids is reduced to a sufficiently low value, thus, emulsification takes place and permits stability of minute droplets of oil in the bulk of water (or vice versa). The emulsifying power of the prepared surfactants in terms of time needed for the separation of 9 mL of the solution is presented in Table 3a. In accordance with the interfacial tension measurements (*vide supra*), the data show that, the stability of the formed emulsion decreases as the number of propylene oxide units increases. Obviously, the solubility of the surfactant in the oil phase decreases as the hydrophilic part ($n$) increases, resulting in weaker emulsion [53, 54]. Generally, the measured time ranged between 36 and 55 min, thus, indicating moderate emulsifying properties for the synthesized surfactants.

*CMC Measurements*

The CMC measures the efficiency of surfactants, it indicates the amount of surfactant required to reach maximum surface tension reduction. A surfactant having a low CMC value enjoys excellent wetting, emulsifying, solubilizing and detergency properties. Within a given series of structurally related surfactants, factors that lead to a decrease in the surface tension are expected to decrease the CMC value. As outlined in Table 3a, b, the surface tension, CMC values and the surface tension at the critical micelle concentration ($\gamma_{CMC}$) measured for **I(a–c)**–**IX(a–c)** increase as the propylene oxide units increases. Within each series of surfactants, noting that the hydrophobic part is unchanged, the smallest CMC value is reached where $n = 3$, i.e., when the adhesive force is at its least (Graphs of surface tension vs log of concentration of added surfactant, used in the determination of the CMC are presented in the supplementary material section). Previous reports agree with our results [55].

*Effectiveness ($\pi_{CMC}$)*

The effectiveness of a surfactant ($\pi$) is measured by its ability to induce the maximum reduction in the surface tension. Since the CMC point presents the minimum surfactant concentration needed to produce the maximum reduction in surface tension; consequently, the effectiveness of a surfactant ($\pi_{CMC}$) can be measured from the decrease in the surface tension of pure water ($\gamma_0$) that is induced by this surfactant at the CMC [32]. Logically, effectiveness of the prepared surfactants decreases as ($\gamma_{CMC}$) increases, Table 3b.

*Efficiency ($PC_{20}$)*

In solution, surfactants lower the surface tension due to their adsorption in between water molecules. Thus, the performance of a surfactant can also be discussed in terms of its efficiency of adsorption. This is usually defined as the surfactant adsorption efficiency, which is the concentration of a surfactant required to produce a 20 mN/m reduction in surface tension. It is designated by $PC_{20}$ and can be calculated by Eq. 2 (*vide supra*) [33]. The larger $PC_{20}$ the more efficiently the surfactant is adsorbed at the interface and the more efficiently it reduces surface tension. In accordance of the above mentioned results, values of $PC_{20}$ for the prepared

surfactants are found to decrease by increasing the number of propylene oxide units (cf Table 3a, b).

*Maximum Surface Excess $\Gamma_{max}$*

The extent of surfactant adsorption at a liquid surface is expressed in terms of its surface excess concentration, Γ. This is defined as the excess of surfactant present per unit area of surface over what would be present if uniform surfactant concentration existed right up to the surface. Surface excess concentration $\Gamma_{max}$, is related to surface tension by the Gibbs equation, Eq. 3 [33] and to its maximum surface concentration CMC, and efficiency by the following equation (Eq. 6) by Rosen [56].

$$\pi_{CMC} = 20 + 2.303nRT\Gamma_{max} \log\left[\frac{C_{CMC}}{C_{\pi} - 20}\right] \quad (6)$$

The data obtained from applying Eq. 3 are presented in Table 3b. It indicated that the maximum surface excess increased by increasing the number of propylene oxide units and ranged between 0.79 and 2.57 mol/cm$^2$.

*Minimum Surface Area ($A_{min}$)*

The area per surfactant molecule $A_{min}$ at the air/water interface at surface saturation provides information about the degree of packing and the orientation of the adsorbed surfactant molecule [35, 36]. The calculated average areas $A_{min}$ are given in Table 3b. Within a series of surfactants, increasing the number of propylene oxide units results in a significant decrease in $A_{min}$. This indicates that higher order of packing is induced upon increasing ($n$).

*Resistance to Hydrolysis*

Surfactants are intensively used in the manufacture of detergents, consequently, the stability of a certain surfactant towards acids and bases is a crucial factor in its utilization. Table 4 presents the results obtained from testing the

**Table 5** Biodegradability of the synthesized surfactants

| Compd. | No. of moles[a] | 1st Day | 2nd day | 3rd Day | 4th Day | 5th day | 6th day | 7th day |
|---|---|---|---|---|---|---|---|---|
| **I(a–c)** | 3 | 63 | 67 | 75 | 84 | 92 | – | – |
| | 5 | 55 | 64 | 69 | 80 | 88 | 91 | – |
| | 7 | 47 | 58 | 66 | 77 | 45 | 94 | – |
| **II(a–c)** | 3 | 51 | 62 | 77 | 84 | 94 | – | – |
| | 5 | 46 | 54 | 68 | 71 | 84 | 91 | – |
| | 7 | 41 | 52 | 65 | 67 | 81 | 88 | – |
| **III(a–c)** | 3 | 49 | 58 | 67 | 75 | 82 | 87 | – |
| | 5 | 46 | 51 | 58 | 69 | 76 | 84 | – |
| | 7 | 41 | 52 | 56 | 67 | 72 | 83 | 91 |
| **IV(a–c)** | 3 | 53 | 69 | 74 | 83 | 97 | – | – |
| | 5 | 49 | 62 | 67 | 78 | 85 | 92 | – |
| | 7 | 46 | 55 | 57 | 66 | 76 | 89 | – |
| **V (a–c)** | 3 | 53 | 66 | 75 | 85 | 95 | – | – |
| | 5 | 48 | 60 | 68 | 78 | 91 | – | – |
| | 7 | 45 | 50 | 62 | 74 | 83 | 93 | – |
| **VI(a–c)** | 3 | 56 | 68 | 79 | 86 | 96 | – | – |
| | 5 | 53 | 62 | 69 | 85 | 94 | – | – |
| | 7 | 51 | 60 | 66 | 84 | 93 | – | – |
| **VII(a–c)** | 3 | 50 | 60 | 77 | 84 | 94 | – | – |
| | 5 | 46 | 54 | 68 | 71 | 84 | 95 | – |
| | 7 | 41 | 52 | 65 | 67 | 80 | 93 | – |
| **VIII(a–c)** | 3 | 51 | 62 | 78 | 86 | 93 | – | – |
| | 5 | 46 | 55 | 69 | 73 | 85 | 91 | – |
| | 7 | 42 | 54 | 66 | 69 | 80 | 90 | – |
| **IX(a–c)** | 3 | 54 | 61 | 73 | 81 | 90 | – | – |
| | 5 | 51 | 60 | 77 | 84 | 91 | – | – |
| | 7 | 47 | 58 | 66 | 78 | 85 | 92 | – |

[a] Number of propylene oxide units

resistance of the synthesized surfactants towards acidic and alkaline hydrolysis. In an acidic medium, compounds **I(a–c)** to **IX(a–c)** show high stability when boiled for 30 min, but they are less stable upon boiling for 60 min. On the other hand, in an alkaline medium, the synthesized surfactants are only slightly affected even after boiling for 60 min. Therefore, we concluded that, it would be safe to use the synthesized surfactants in the manufacture of detergents.

*Biodegradability of the Synthesized Surfactants*

Biodegradation is the destruction of a chemical by the metabolic activity of microorganisms. Since surfactants are susceptible to biodegradation and in order to examine their effect on water pollution, the biodegradation of the synthesized nonionic surfactants was evaluated by the conventional River Die-Away test employing the surface-tension technique as an analytical tool [57, 58]. The biodegradability data are presented in Table 5. Within experimental accuracy, all the prepared nonionic surfactants seem to degrade easily. The results showed that, 40–50 % of the surfactants was biodegradable within the first day, further degradation occurred on the next days until it died away on the 6th day. Consequently, these compounds are safe for human beings and the environment. It should be noted that, since the studied compounds share the same hydrophobic part, then, the extent of biodegradation encountered for these compounds depends mainly on the number of propylene oxide units. Consequently, it can be concluded that the biodegradability of a certain surfactant decreases by increasing the number of propylene oxide units.

## Conclusions

New oxadiazole, thiadiazole and triazole derivatives (**1–12**) have been successfully synthesized. All the synthesized compounds (**1–12**) exhibited moderate to high activity toward tested $G^-$, $G^+$ bacteria, while some of them (**6**, **7**, **10**, **11**) exhibited good antifungal activity. New classes of nonionic surface active agents containing heterocyclic moieties were synthesized via subjecting the synthesized compounds to different quantities of propylene oxide. All the new nonionic surfactants displayed good surface active properties that are affected by the size of the hydrophilic part. The lower the number of propylene oxide units, the more effective is the surfactant in decreasing the surface and interfacial tension. Consequently, the lower the values of CMC and $\Gamma_{max}$are, the higher is the emulsion stability, effectiveness ($\pi_{CMC}$), efficiency ($PC_{20}$) and minimum surface area ($A_{min}$). In addition, the synthesized surfactants showed good tolerance towards acidic and alkaline media and good degradation susceptibility within 7 days. As a consequence, the synthesized compounds and surfactants are safe for human beings as well as the environment. They can be used in the manufacture of drugs, cosmetics, moderate emulsifiers, wetting agents, textiles and dyes.

## References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