Synthesis, characterization and spectral studies of various newer long chain aliphatic Acid (2-hydroxy benzylidene and 1H-indol-3-ylmethylene) hydrazides as mosquito para-pheromones

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INTRODUCTION

Acyl derivatives of hydrazine are called acid hydrazides. They constitute an important class of biologically active organic compounds. Hydrazides and their condensation products are reported to possess a wide range of antibacterial activity\(^1\)\(^2\) and tuberculostatic\(^3\)\(^4\) properties. Similarly derivatives of aryloxyacetyl hydrazides have antituberculotic activities and some are used as post-emergence, selective
herbicides to control terrestrial and aquatic broad leaved weeds in some plants. Another classical application of hydrazines and hydrazides is in the synthesis of heterocycles, and many heterocycles are precursors of drugs, agrochemicals and dye stuffs and are therefore of commercial importance. Some hydrazines were reported as newer class of insecticidal insect growth regulators. Tebufenozide, methoxyfenozide and chromafenozide are commercialized member of the novel group of diacylhydrazine insect growth regulators. From the synthetic point of view, hydrazones are important synthones for several transformations and their synthesis from various precursors is well documented. Various long chain acids and esters are reported as semiochemicals of egg origin that affect the ovipositional behavior of the mosquito Aedes aegypti, which is a vector of dengue, chikungunya and yellow fever. Similarly, substantial documentation is available for oviposition-stimulating semiochemicals such as n-henesicosane, trimethylphenol, 4-methylphenol, 3-methylindole.

Over the last few years, there has been growing interest in the synthesis of organic compounds under green chemistry such as microwave irradiation because of increasing environmental consciousness. The feasibility of microwave assisted synthesis has been demonstrated in various transformations like condensation, cycladdition, alkylation, synthesis of various heterocyclic compounds and in many other chemical reactions. The salient features of these transformations are the enhanced reaction rate, greater selectivity and the experimental ease of manipulation leading to an efficient, environmentally friendly & cost effective pathway of several synthetically useful compounds. Keeping in view of the biological and synthetic utility of hydrazides, long chain aliphatic esters and acids, we have synthesized newer long chain acid hydrazides and corresponding substituted hydrazides using microwave irradiation technique as well as by conventional method (Scheme 1 & 2). The synthesis of these substituted hydrazides assumes importance because of its utility from social perspective. All the above compounds were characterized by spectral analysis.

RESULTS AND DISCUSSION

Hydrazinolysis of various carboxylic acid hydrazides \( (\text{CH}_2\text{-(CH}_2\text{)}_n\text{CO-NH-NH}_2, n=10, 12, 14) \) from corresponding methyl ester was carried out by conventional method as well as by microwave technique. The conventional method involved the refluxing of methyl ester of carboxylic acid with excess of hydrazine hydrate in ethanol medium for 3-4 hours while in case of the microwave technique, a mixture of ester and hydrazine hydrate (1:1 molar ratio) was irradiated with microwave for 10-15 minutes without any solvent, catalyst or solid support. The

Table 1. Synthesis of various long chain aliphatic acid hydrazides

<table>
<thead>
<tr>
<th>Product</th>
<th>Conventional (hr)</th>
<th>MW (min)</th>
<th>Yield of the product (%)</th>
<th>Conventional</th>
<th>MW</th>
</tr>
</thead>
<tbody>
<tr>
<td>2a</td>
<td>4</td>
<td>9</td>
<td>65</td>
<td>85</td>
<td></td>
</tr>
<tr>
<td>2b</td>
<td>4</td>
<td>10</td>
<td>55</td>
<td>87</td>
<td></td>
</tr>
<tr>
<td>2c</td>
<td>4</td>
<td>10</td>
<td>65</td>
<td>85</td>
<td></td>
</tr>
</tbody>
</table>

*isolated product

Table 2. Physical & spectral data for compound 2b-c

<table>
<thead>
<tr>
<th>Comp</th>
<th>mp (°C)</th>
<th>Mol. formula</th>
<th>( \delta_0 (\text{in } \text{Hz}) )</th>
<th>MS (M+)</th>
</tr>
</thead>
<tbody>
<tr>
<td>2a</td>
<td>105-108</td>
<td>C_{27}H_{50}N_2O</td>
<td>0.9(t, 3H, J 7.0), 1.2(conglomerate, 16H, 8CH_2), 2.1(p, 2H, CH_2, J 7.0)</td>
<td>241</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>2.8(t, 2H, CH_3CO, J 6.0), 3.9(bs, 2H, NH_3), 6.8 (s, 1H, NHCO, exchangeable)</td>
<td></td>
</tr>
<tr>
<td>2b</td>
<td>106-110</td>
<td>C_{26}H_{48}N_2O</td>
<td>1.0(t, 3H, J 7.0), 1.4(conglomerate, 20H, 10CH_2), 2.5(p, 2H, CH_2, J 7.0), 2.3(t,</td>
<td>242</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>2H, CH_3CO, J 6.0), 3.7(bs, 2H, NH_3), 6.9(s, 1H, NHCO, exchangeable)</td>
<td></td>
</tr>
<tr>
<td>2c</td>
<td>112-114</td>
<td>C_{32}H_{62}N_2O</td>
<td>0.9(t, 3H, J 7.0), 1.3(conglomerate, 24H, 12CH_2), 2.0 (p, 2H, CH_2, J 7.0),</td>
<td>270</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>2.5(2H, CH_3CO, J 6.0), 3.8(bs, 2H, NH_3), 6.7</td>
<td></td>
</tr>
</tbody>
</table>

*IR: 3350 cm^{-1} (NH), this IR band was absent in the case of compounds 3a-f
**All the compounds gave satisfactory elemental analyses: (C, H, and N within ± 0.32% of calcd values)
results obtained from two approaches are summarized in Table 1 (Entries 2a-c).

Various newer carboxylic acid (2-hydroxy benzylidene) hydrazide (3a, 3e, 3e) and carboxylic acid (1H-indol-3-ylmethylene) hydrazide (3b, 3d, 3f) were also prepared by condensation of 2a-c with 2-hydroxy benzaldehyde and indole-3-carboxaldehyde respectively under conventional as well as microwave
irradiation methods. In conventional method, they were prepared by refluxing 1a-c with different aldehydes in ethanol and in microwave irradiation technique; they were prepared without using any solvent. The overall yield of the product using microwave irradiation technique was 85-90% as compared to the conventional methods in which the yields were 30-55% and reaction time was 3-10 min by microwave irradiation as compared to 4-5 hour in conventional method.

**Spectral Analysis**

IR spectrum of dodecanoic acid hydrazide (2a) showed absorption band at 1635 and 1500 cm\(^{-1}\) corresponding to C=O and C-N stretching vibrations. Two bands at 3350 and 3310 cm\(^{-1}\) appeared due to the presence of NH\(_2\) and NH groups respectively. The corresponding dodecanoic acid (2-hydroxybenzylidene) hydrazide showed similar spectra except that bands due to the NH\(_2\) group, it showed band at 1575-1565 cm\(^{-1}\) due to the C=N stretching vibrations. The \(^1\)H NMR spectrum of dodecanoic acid hydrazide displayed a broad singlet at 4.2 (2H) corresponding to NH\(_2\) protons. Methyl proton CH\(_3\) displayed a triplet at 0.9 in its \(^1\)H NMR spectrum while a singlet at 13.8 ppm in its \(^13\)C NMR spectrum. A singlet appeared at \(\delta\) 8.2 ppm due to the NHCO proton. Presence of later was further supported by the appearance of a peak at 171.80 in its \(^13\) C NMR spectrum. CH\(_2\)-CO proton displayed a triplet at 2.5 in its \(^1\)H NMR while a singlet appeared at 39.3 ppm in its \(^13\) C NMR. A distorted quintet was appeared at 1.4 in \(^1\)H NMR. The remaining CH\(_3\) groups, which were very similar in chemical shift, were strongly coupled to one another; they appeared as partially resolved band and act as a conglomerate of spins in coupling to the CH\(_3\) group & signal appeared at 1.2 in its \(^1\)H NMR. Similar pattern for the proton resonance was also observed in the \(^1\)H NMR spectrum of substituted hydrazides (hydrazones). The corresponding substituted hydrazides (hydrazones) of 2a containing phenolic moiety (3a) displayed singlet corresponding N=CH proton at \(\delta\) 8.0-8.4 while four benzenoid protons appeared as multiplet at 6.9-7.5 ppm. Similar pattern for the resonance was observed in the \(^1\)H NMR spectrum of substituted hydrazide (3b) having indolic moiety and displayed a singlet at 10.1 resonated due to indole NH proton. Four benzenoid protons and one indolic CH proton appeared as multiplet at 7.1-7.7 ppm. In the EI mass spectra of dodecanoic acid hydrazide (2a), molecular ion peak was weak but usually discernible and for the corresponding substituted hydrazides (hydrazones) 3a & 3b, molecular ion peaks were distinct in the mass spectra. Fragment ion peak at \(m/z\) 183 could be attributed to the loss of NHNH\(_2\) and NHN=CH-Ar radicals from the molecular ions of dodecanoic acid hydrazide (2a) and dodecanoic acid (2-hydroxybenzylidene) hydrazide (3a) & dodecanoic acid (1H indol-3-ylmethylene) hydrazide (3b) respectively. The formation of fragment ion at \(m/z\) 74 can be rationalized by the loss of neutral molecule 1-decene from molecular ion (2a) as depicted in Scheme 3. The base peak at \(m/z\) 57 could arise due to the loss of methyl radical and H\(_2\) molecule from the fragment ion having \(m/z\) value of 74 (Scheme 3). The fragment ion peak at \(m/z\) 199 could be attributed to the loss of CH\(_4\) radical from the molecular ion of dodecanoic acid hydrazide (2a). The ions corresponding to \(m/z\) 185, 171, 157, 143, 129, 115, 101, 87, 73 were formed due to loss of CH\(_3\) group successively. In addition, Mc-Lafferty rearrangement in molecular ion of 3a gave rise to peak at \(m/z\) 178 and peaks at \(m/z\) 163, 135, 107 were due to successive loss of CH\(_3\) radical, CO & N\(_2\) molecules. Similarly the formation of fragment ion at \(m/z\) 201 can be rationalized by the loss of neutral molecule dodecene from molecular ion 3b which in turn gave rise to peaks at 186 & 158 due to subsequent loss of CH\(_3\) radical and CO mole-
cule. The base peak at m/z 142 could arise due to the loss of neutral molecule tetradeconoic acid amide from molecular ion 3b.

CONCLUSION

In summary, we described the microwave assisted synthesis of long chain acid hydrazides and various newer corresponding benzylidene hydrazides & indolylmethylene hydrazides and compared with conventional method. Spectral properties and mass spectral fragmentation pattern of these hydrazides & hydrazones were also discussed. It has been found that some of these hydrazides have attractant activity and some have repellent activity depending on their concentration against mosquitoes and we will be published somewhere else.19

EXPERIMENTAL

General

All the reagents and solvent were obtained from commercial sources and used without further purification. Melting points were taken in open capillary in an electro thermal point apparatus and are uncorrected. IR spectra were recorded as KBr pellet using Perkin Elmer Spectrum BX FT-IR spectrophotometer, 1H NMR spectra in CDCl3/DMSO-d6 on a Bruker Avance (400MHz) spectrometer using TMS as internal reference. 13C NMR spectra were recorded on the same instrument at 100MHz using the same solvent and internal reference. Chemical
shift is reported in δ (PPM). Mass spectra were recorded on a Finnigan matt TSQ 700 mass spectrometer. The progress of all reactions was monitored by TLC on 2.0×5.0-cm aluminum sheets precoated with silica gel to a thickness of 0.25-mm (Merck). Microwave assisted syntheses were carried out in Samsung CK 138 F domestic microwave oven.

**Dodecanoic acid hydrazide 2a**
Methyl dodecanoate (10 mmol) was dissolved in 99% hydrazine hydrate (10 mmol) in a conical flask and was placed in domestic microwave oven. After irradiation at 180 Watt for 10 minutes, the solid product was recrystallized from ethanol to give dodecanoic acid hydrazide 2a (85% yield) (Table 1 & 2).

**General procedure for the synthesis of long chain aliphatic acid (2-hydroxy benzylidene) hydrazides & (1H-indol-3-ylmethylene) hydrazides**

**Conventional synthesis**
To a stirred solution of carboxylic acid hydrazide (5 mmol) in ethanol was added aldehyde (5 mmol) and the reaction mixture was refluxed for 3-4 hrs. After completion of the reaction, solvent was evaporated & solid product was separated, filtered, dried, & recrystallized from ethanol.

**Microwave assisted synthesis**
Carboxylic acid hydrazide (5 mmol) was mixed with aldehyde (5 mmol) in a conical flask and the mixture was irradiated with microwave irradiation in microwave oven for specified period (300 Watt). The reaction was monitored by TLC. After completion of the reaction, the solid product was recrystallized from ethanol to give the pure substituted hydrazides (hydrazones).

**Dodecanoic acid (2-hydroxy benzylidene) hydrazide 3a**
Mp: 108-110 ºC, IR (KBr): 3432, 3238, 2922, 1670, 1567, 1491, 1390, 753 cm\(^{-1}\). \(^1\)H NMR (400 MHz, DMSO-d\(_6\)) δ =10.8 (s, 1H, OH), 8.5 (s, 1H, CONH, exchangeable), 8.0 (s, 1H, N=C=CH), 6.9-7.5 (m, 4H, Ar-H), 0.9 (t, 3H, CH\(_3\)), 1.2 (conglomerate, 16H, CH\(_2\)), 1.4 (p, 2H, CH\(_2\)), 2.5 (t, 2H, CH\(_2\)CO), MS: m/z (%) 318 (40), [C\(_{10}\)H\(_{13}\)N\(_2\)O\(_2\)]\(^+\), 275 (12), 219 (10), 191 (14), 178 (25), 136 (100), 135 (79), 119 (71), 107 (47), 93 (16), 91 (30), 65 (26).

**Dodecanoic acid (1H-indol-3-ylmethylene) hydrazide 3b.**
Mp: 145-147 ºC, IR (KBr): 3245, 3055, 2924, 1638, 1597, 1443, 1246, 992, 740 cm\(^{-1}\). \(^1\)H NMR (400 MHz, DMSO-d\(_6\)) δ =10.1 (s, 1H, NH indole, exchangeable), 8.8 (s, 1H, CONH, exchangeable), 8.5 (s, 1H, N=CH), 7.0-7.8 (m, 4 x Ar-H, 1 x indole CH), 2.1 (t, 2H, CH\(_2\)CO) 1.6 (p, 2H, CH\(_2\)), 1.2 (conglomerate, 16H, CH\(_2\)) MS: m/z (%) 341 (41), [C\(_{16}\)H\(_{17}\)N\(_2\)O\(_2\)]\(^+\), 228 (45), 201 (13), 186 (5), 185 (4), 184 (6), 159 (48), 158 (4), 157 (15), 155 (4), 142 (100), 130 (25), 116 (24), 114 (14), 59 (38).

**Tetradecanoic acid (2-hydroxy benzylidene) hydrazide 3c.**
Mp: 113-115 ºC, IR (KBr): 3447, 3138, 2920, 1657, 1491, 1390, 753 cm\(^{-1}\). \(^1\)H NMR (400 MHz, DMSO-d\(_6\)) δ =10.7 (s, 1H, OH), 8.4 (s, 1H, CONH, exchangeable), 8.1 (s, 1H, N=CH), 7.1-7.9 (m, 4H, Ar-H), 1.1 (t, 3H, CH\(_3\)), 1.5 (conglomerate, 20H, CH\(_2\)), 1.9 (p, 2H, CH\(_2\)), 2.2 (t, 2H, CH\(_2\)CO), MS: m/z (%) 346 (16), [C\(_{18}\)H\(_{21}\)N\(_2\)O\(_2\)]\(^+\), 219 (8), 233 (4), 219 (5), 205 (4), 191 (10), 178 (15), 177 (4), 163 (6), 136 (100), 135 (79), 120 (65), 119 (57), 107 (34), 99 (7), 93 (13), 91 (30), 71 (45), 65 (26), 59 (100), 43 (73).

**Tetradecanoic acid (1H-indol-3-ylmethylene) hydrazide 3d.**
Mp: 154-156 ºC, IR (KBr): 3210, 3025, 2923, 1642, 1447, 1357, 1246, 995, 744 cm\(^{-1}\). \(^1\)H NMR (400 MHz, DMSO-d\(_6\)) δ =10.4 (s, 1H, NH indole, exchangeable), 8.4 (s, 1H, CONH, exchangeable), 8.0 (s, 1H, N=CH), 7.2-7.9 (m, 4 x Ar-H, 1 x indole CH), 2.3 (t, 2H, CH\(_2\)CO), 1.9 (p, 2H, CH\(_2\)), 1.4 (conglomerate, 20H, CH\(_2\)), 0.9 (t, 3H, CH\(_3\)) MS: m/z (%) 369 (54), [C\(_{20}\)H\(_{23}\)N\(_2\)O\(_2\)]\(^+\), 228 (45), 211 (4), 201 (5), 186 (5), 185 (4), 184 (6), 159 (74), 158 (14), 157 (15), 155 (4), 142 (100), 130 (25), 116 (20), 114 (14), 59 (40).

**Hexadecanoic acid (2-hydroxy benzylidene) hydrazide 3e.**
Mp: 118-120 ºC, IR (KBr): 3440, 3038, 2921, 1670, 1560, 1466, 1278, 752 cm\(^{-1}\). \(^1\)H NMR (400 MHz, DMSO-d\(_6\)) δ =10.3 (s, 1H, OH), 8.8 (s, 1H, CONH, exchangeable), 8.5 (s, 1H, N=CH), 7.0-7.8 (m, 4H, Ar-H), 0.9 (t, 3H, CH\(_3\)), 1.3 (conglomerate, 24H,
Hexadecanoic acid(1H-indol-3-ylmethylene) hydrazide 3f.

Mp: 160-162 ºC, IR (KBr): 3227, 3055, 2916, 1638, 1617, 1361, 1247, 991, 739 cm\(^{-1}\).

\[ \text{H NMR (400 MHz, DMSO-d}_6\):} \delta = 10.2 (s, 1H, NH indole, exchangeable), 8.5 (s, 1H, CONH, exchangeable), 8.0 (s, 1H, N=CH), 7.0-7.8 (m, 4 x Ar-H, 1 x indole CH), 2.1 (t, 2H, CH\(_2\)CO), 1.5 (p, 2H, CH\(_2\)), 1.2 (conglomerate, 20H, CH\(_2\)), 0.9 (t, 3H, CH\(_3\))

Acknowledgements. Authors sincerely thank Er K Sekhar, Director, Defence Research and Development Establishment, Gwalior for keen interest and encouragement. We are also thankful to Dr. D.K. Dubey for his valuable suggestions & comments and to Dr. Semwal for recording spectra.

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