Journal of the Korean Chemical Society
2007, *Vol. 51, No. 6*
Printed in the Republic of Korea

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

Suman Awasthi*, Poonam Rishishwar, Ambati N. Rao, Kumaran Ganesan, and Ramesh Chandra Malhotra

Synthetic Chemistry Division, Defence Research & Development Establishment, Jhansi Road, Gwalior 474002 India

(2007. 4. 3 접수)

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

Suman Awasthi*, Poonam Rishishwar, Ambati N. Rao, Kumaran Ganesan, and Ramesh Chandra Malhotra

Synthetic Chemistry Division, Defence Research & Development Establishment, Jhansi Road, Gwalior-474002 India

(Received April 3, 2007)

요 약. 여러가지 긴 사슬 지방산 하이드라지드는 방향족과 헤테로 고리 알데히드와 반응하여 알코올 용매하에서 2-hydroxy benzylidene와 새로운 모기 파라-페로몬인1H-indol-3-ylmethylene hydrazides을 얻었다. 마이크로파의 조사기술과 마찬가지로 전통적인 방법에 의한 다양한 새로운 긴고리 지방산 하이드라지드 (2-hydroxy benzylidene와 1H-indol-3-ylmethylene)의 합성방법도 보고한다. 이 화합물들의 구조는 FTIR, NMR & MS와 같은 분광학적 기법에 의해 증명되었다. 이 화합물의 전자충격질량스펙트럼 분쇄 패턴의 몇 가지 재미있는 특징도 논의했다.

주제어: 긴 사슬 지방산 하이드라지드, 긴 사슬 지방산(2-hydroxy benzylidene& 1H-indol-3-ylmethylene) 하이드라지드, 모기 파라-페로몬, 마이크로파

ABSTRACT. Various long chain aliphatic acid hydrazides react with aromatic and heterocyclic aldehydes in alcoholic medium in refluxing conditions to give corresponding 2-hydroxy benzylidene and 1H-indol-3-ylmethylene hydrazides, a newer class of mosquito para-pheromones. We describe here synthesis of various novel long chain aliphatic acid (2-hydroxy benzylidene and 1H-indol-3-ylmethylene) hydrazides by conventional as well as microwave irradiation techniques. The structures of these compounds have been confirmed by spectroscopic techniques (FTIR, NMR & MS). Some of the interesting features of the electron impact mass spectral fragmentation pattern of these compounds have also been discussed.

Keywords: Long Chain Aliphatic Acid Hydrazide, Long Chain Aliphatic Acid (2-hydroxy benzylidene & 1H-indol-3-ylmethylene) Hydrazide, Mosquito Para-pheromones, Microwave

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 posses 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[5] 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.[6] From the synthetic point of view, hydrazones are important synthones for several transformations and their synthesis from various precursors is well documented.[7] Various long chain acids and esters are reported as semiochemicals of egg origin that affect the ovipositional behavior of the mosquito *Aedes aegypti*,[8] which is a vector of dengue, chikungunya and yellow fever. Similarly, substantial documentation is available for oviposition-stimulating semiochemicals such as n-heneicosane,[9] trimethylphenol, 4-methylphenol,[10] 3-methylindole.[11]

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,[12] cycloaddition,[13] alkylation,[14] synthesis of various heterocyclic compounds[15-17] 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[18] leading to an efficient, environmental 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 (**2a-c,** *Table* 1) and corresponding substituted hydrazides (**3a-f,** *Table* 3) 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.

Table 1. Synthesis of various long chain aliphatic acid hydrazides

Product	Time		Yield of the product (%)[a]	
	Conventional (hr)	MW (min)	Conventional	MW
2a	4	9	65	85
2b	4	10	55	87
2c	4	10	65	85

[a] isolated product

RESULTS AND DISCUSSION

Hydrazinolysis of various carboxylic acid hydrazides [CH_3-$(CH_2)_n$-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

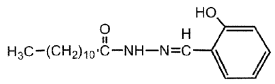
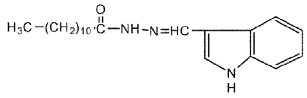
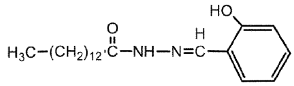
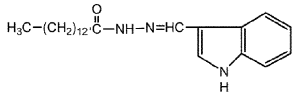
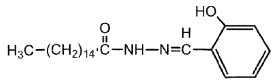
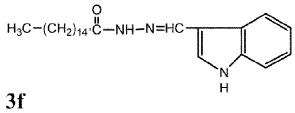
Table 2. Physical & spectral data for compound 2b-c

Comp	mp (°C)	Mol. formula[++]	δ_H (*J* in Hz)	MS (M^+)
2a[+]	103-105	$C_{12}H_{26}N_2O$	0.9(t, 3H, *J*, 7.0), 1.2(conglomerate, 16H, $8CH_2$), 2.1(p, 2H, CH_2, *J*, 7.0), 2.8(t, 2H, CH_2CO, *J*, 6.0), 3.9(bs, 2H, NH_2), 6.8 (s, 1H, NHCO, exchangeable)	214
2b[+]	108-110	$C_{14}H_{30}N_2O$	1.0(t, 3H, *J*, 7.0), 1.4(conglomerate, 20H, $10CH_2$), 1.9(p, 2H, CH_2, *J*, 7.0), 2.3(t, 2H, CH_2CO, *J*, 6.0), 3.7(bs, 2H, NH_2), 6.9(s, 1H, NHCO, exchangeable)	242
2c[+]	112-114	$C_{16}H_{34}N_2O$	0.9(t, 3H, *J*, 7.0), 1.3(conglomerate, 24H, $12CH_2$), 2.0 (p, 2H, CH_2, *J*, 7.0), 2.5(t,2H, CH_2CO, *J*, 6.0), 3.8(bs, 2H, NH_2), 6.7	270

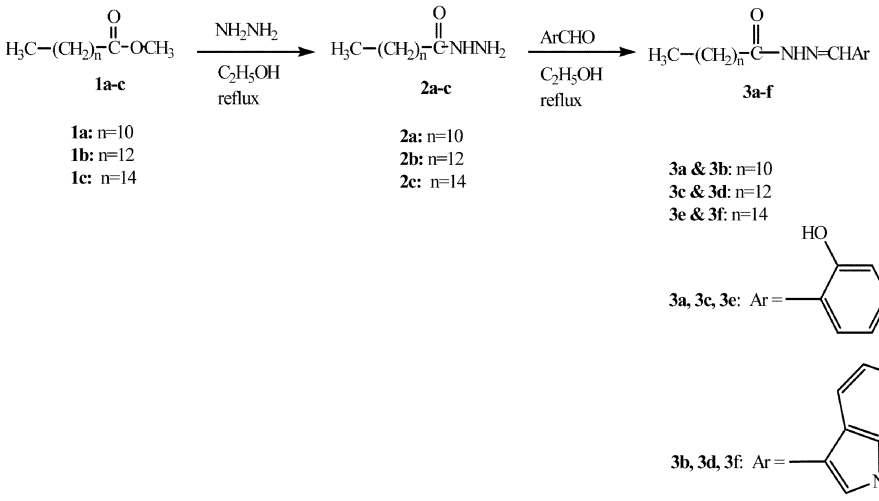
[+] IR: 3350 cm^{-1}(NH_2), this IR band was absent in the case of compounds 3a-f

[++] All the compounds gave satisfactory elemental analyses: (C, H, and N within = 0.32% of calcd values)

Table 3. Synthesis of various long chain aliphatic acid (2-hydroxy benzylidene) hydrazides & (1H-indol-3-ylmethylene) hydrazides

Product	Time		Yield of the product[a]	
	Conventional (hr)	MW (min)	Conventional	MW
 **3a**	3.0	12	67	89
 **3b**	4.0	15	55	85
 **3c**	3.0	13	62	87
 **3d**	4.0	16	53	83
 **3e**	3.0	13	63	86
 **3f**	4.0	16	50	80

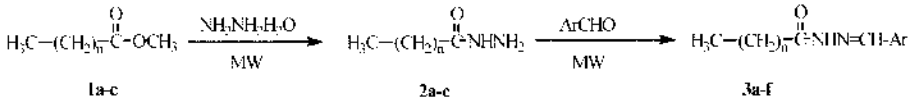
[a]isolated product



Scheme 1. Conventional synthesis of acid hydrazide.

results obtained from two approaches are summarized in *Table* 1 (Entries **2a-c**).

Various newer carboxylic acid (2-hydoxybezylidene) hydrazide (**3a, 3c, 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

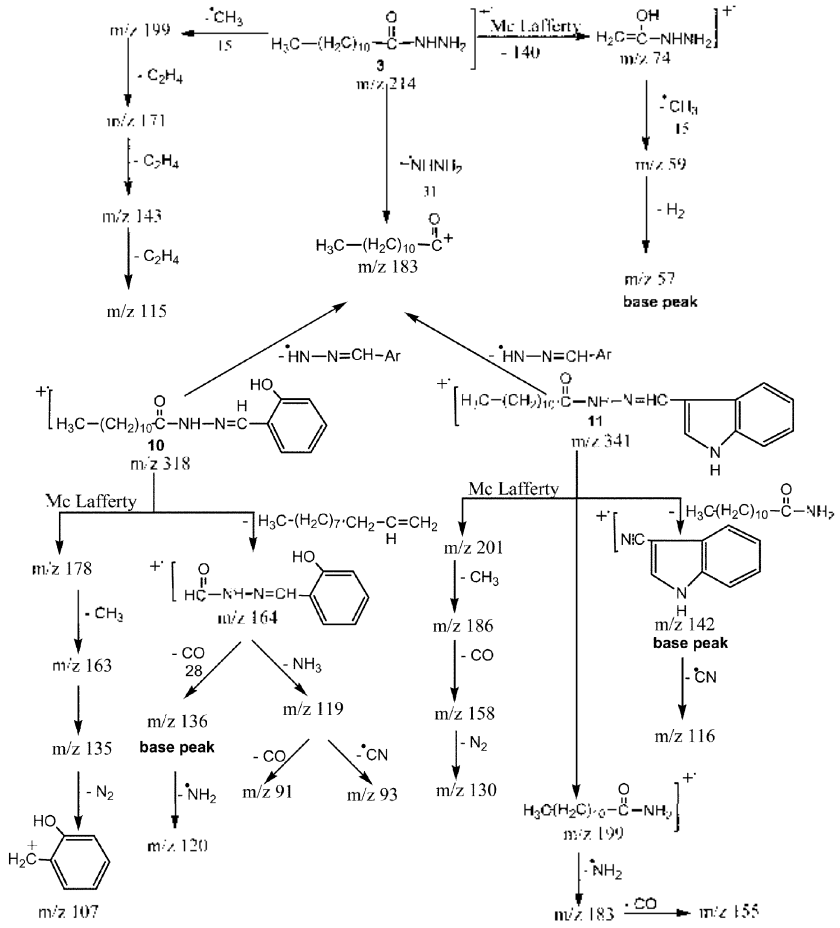


Scheme 2. Microwave assisted synthesis of acid hydrazides.

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-hydroxybenzyldene) 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 ^1H 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 ^1H NMR spectrum while a singlet at 13.8 ppm in its ^{13}C NMR spectrum. A singlet appeared at δ 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 ^1H NMR while a singlet appeared at 39.3 ppm in its ^{13}C NMR. A distorted quintet was appeared at 1.4 in ^1H NMR. The remaining CH_2 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 ^1H NMR. Similar pattern for the proton resonance was also observed in the ^1H NMR spectrum of substituted hydrazides (hydrazones). The corresponding substituted hydrazides (hydrazones) of 2a containing phenolic moiety (**3a**) displayed singlet corresponding N=CH proton at δ 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 ^1H 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_3 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_2 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-



Scheme 3. Analysis of mass spectra of substituted acid hydrazides (hydrazones).

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, ^{1}H NMR spectra in $CDCl_3$/DMSO-d_6 on a Bruker Avance (400MHz) spectrometer using TMS as internal reference. ^{13}C 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 washed with the 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 ℃, IR (KBr): 3432, 3238, 2922, 1670, 1560, 1525, 1380, 758 cm^{-1}. ^1H NMR (400 MHz, DMSO-d_6) δ =10.8 (s, 1H, OH), 8.5 (s, 1H, CONH, exchangeable), 8.0 (s, 1H, N=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_2CO), MS: m/z (%) 318 (40), $[C_{19}H_{30}N_2O_2]^+$, 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 ℃, IR (KBr): 3245, 3055, 2924, 1638, 1597, 1443, 1246, 992, 740 cm^{-1}. ^1H 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_2CO) 1.6 (p, 2H, CH_2), 1.2 (conglomerate, 16H, CH_2), 1.0(t, 3H, CH_3) MS: m/z (%) 341 (41), $[C_{21}H_{27}N_3O]^-$, 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 ℃, IR (KBr): 3447, 3138, 2920, 1670, 1567, 1491, 1390, 753 cm^{-1}. ^1H NMR (400 MHz, DMSO-d_6) δ=10.5 (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_2CO), MS: m/z (%) 346 (16), $[C_{21}H_{34}N_2O_2]^+$, 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 ℃, IR (KBr): 3210, 3035, 2923, 1642, 1447, 1357, 1246, 995, 744 cm^{-1}. ^1H NMR (400 MHz, DMSO-d_6) δ=10.0 (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_2CO), 1.9 (p, 2H, CH_2), 1.4 (conglomerate, 20H, CH_2), 0.9 (t, 3H, CH_3) MS: m/z (%) 369 (54), $[C_{23}H_{35}N_3O]^+$, 228 (43), 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 ℃, IR (KBr): 3440, 3038, 2921, 1670, 1560, 1466, 1278, 752 cm^{-1}. ^1H 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,

CH_2), 1.5 (p, 2H, H_2), 2.1 (t, 2H, CH_2CO), MS: m/z (%) 374 (26), $[C_{23}H_{38}N_2O_2]^+$, 345 (3), 331 (4), 317 (4), 303 (3), 289 (3), 247 (4), 219 (5), 191 (10), 179 (5), 178 (25), 163 (6), 136 (100), 120 (65), 119 (57), 107 (34), 99 (11), 93 (10), 91 (20), 71 (25), 65 (16), 59 (50), 43 (30).

Hexadecanoic acid(1H-indol-3-ylmethylene) hydrazide 3f.

Mp: 160-162 °C, IR (KBr): 3227, 3055, 2916, 1638, 1617, 1361, 1247, 991, 739 cm^{-1}. ^1H NMR (400 MHz, DMSO-d_6) δ=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_2CO), 1.5 (p, 2H, CH_2), 1.2 (conglomerate, 20H, CH_2), 0.9 (t, 3H, CH_3) MS: m/z (%) 397 (45), $[C_{23}H_{39}N_2O]^+$, 368 (4), 354 (3), 340 (3), 298 (3), 284 (4), 256 (45), 228 (4), 201(10), 185 (4), 184 (6), 159 (70), 158 (24), 157 (12), 155 (4), 142 (100), 130 (23), 116 (20), 114 (14), 59 (54).

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.

REFERENCES

1. Bonicke, R.; Krach, J. Z. *Hyg Infektionskranch* **1954**, *139*, 140.
2. Haksar, C. N.; Malhotra, R. C.; Pandya G.; Sethi, R. K. *Lab. J. Sc. Technol.*, **1981**, *9B*, 34
3. Binon, F.; Royer, R. *J. Chem. Soc.*, **1953**, 1358.
4. Zikolova, Sv. Farmatoiya, **1965**, *15(4)*, 185.
5. Roman, K. L. Span. Patent, ES 506,945, **1982** (*Chem. Abstr.*, **1985**, *89*, 67124).
6. Dhadialla, T. S.; Carlson, G. R.; Le, D. P. *Annual Review of Entomology* **1998**, *43*, 545-569.
7. Banik, B. K.; Barakat, K. J.; Wagle, W. R.; Manhas, M. S.; Bose, A. K. *J. Org. Chem.*, **1999**, *64*, 5746.
8. Ganesan K.; Mendki, M. J.; Suryanarayana, M. V. S.; Prakash, S.; Malhotra, R. C. *Australian Journal of Entomology*, **2000**, *45*, 75-80.
9. Mendki, M. J.; Ganesan, K.; Prakash, S.; Suryanarayana, M. V. S.; Malhotra, R. C.; Rao, K. M.; Vaidyanathaswamy, R. *Current Science*, **2000**, *78*, 1295-1296.
10. Bentley, M. D.; McDaniel, I. N.; Yatagai, M.; Lee, H. P.; Maynard, R. *Environmental Entomology*, **1979**, *8*, 206-209.
11. Knight, J. C.; Corbet, S. A. *Journal of American Mosquito Control Association*, **1991**, *7*, 37-41.
12. Villemine, D.; Martin, B. *J. Chem. Res.*, **1994**, 146.
13. Lu, Y. F.; Fallis, A. G. *Can. J. Chem.*, **1995**, *73*, 2239.
14. Soriente, A.; Spinella, A.; DeRosa, M.; Giordano, M.; Seettri, A. *Tetrahedron Lett*, **1997**, *38*, 289.
15. Suarez, M.; Loupy, A.; Salfran, E.; Moran, L.; Rolando, E. *Heterocycles*, **1999**, *51*, 21.
16. Goncalo, P.; Roussel, C.; Melot, J. M.; Vebrel, J. *J. Chem. Soc. Perkin Trans 2*, **1999**, 2111.
17. Danks, T. N. *Tetrahedron Lett*, **1999**, *40*, 3957.
18. Verma, R. S. *Green Chemistry*, **1999**, *1*, 43.
19. Rishiswar, P.; Awasthi, S.; Jain, N.; Prakash, S.; Ganesan, K.; Malhotra, R.C.; Vijayaraghavan, R. Ovipositional responses of Aedes aegypti (Diptera: Culicidae) to novel synthesized long chain aliphatic hydrazides (to be communicated to *Vector Ecology*).