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New products

Synthesis and anti-inflammatory activity of benzal-3-pentadecylaryloxyalkyl carboxylic acid hydrazides and 2-benzalamino-5-(3'-pentadecylaryloxyalkyl)-1,3,4-oxadiazoles*

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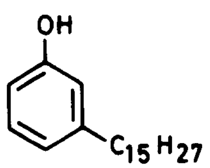
cashew nut shell liquid / cardanol / 3-pentadecylphenol / anti-inflammatory (anti-edematous) activity

Introduction

India is one of the major cashew nut (*Anacardium occidentale* Linn) producing countries of the world, meeting substantial world demand for cashew kernels. The cashew nut shell liquid (CNSL) present in the pericarp of the nut is obtained as a by-product during the roasting of the cashew nuts for the isolation of kernels. Cardanol, a meta-substituted long chain alkyl phenol, is obtained by distillation of CNSL under reduced pressure [1]. The unique feature of cardanol **1** is that on catalytic hydrogenation [2] gives 3-pentadecylphenol **2** (3-PDP) which offers a great chemical maneuverability for the synthesis of variety of compounds.



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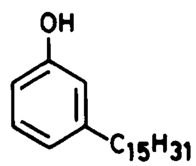

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In view of the fact that synthetic preparation of 3-PDP is very costly [3] and that the availability of CNSL as a by-product is in abundance, it was considered worthwhile to make efforts to explore the 3-PDP incorporated compounds in order to determine their biological activities. The drug analogues [4] from 3-PDP and 3-pentadecyl salicylic acid (tetrahydro anacardic acid) were prepared earlier in view of the lipophilic and less toxic nature of the $C_{15}H_{31}$ side-chain in them, although their biological evaluation was not carried out. Hydrazides, 1,3,4-oxadiazoles and benzal derivatives possess various biological activities. They have been found to exhibit analgesic [5], anti-inflammatory [6] and anti-microbial [7] activities. Recently, we have synthesized and screened 3-pentadecylaryloxyalkyl carboxylic acid hydrazides and their oxadiazole derivatives which showed potent anti-inflammatory activity [8, 9]. The aforementioned facts, prompted us to undertake the present study, which examines the synthesis of a series of new benzal-3-pentadecylaryloxyalkyl carboxylic acid hydrazides and 2-benzalamino-5-(3'-pentadecylaryloxyalkyl)-1,3,4-oxadiazoles to be tested as anti-inflammatory agents.

Chemistry

For the synthesis of the title compounds, 3-pentadecylaryloxyalkyl carboxylic acid hydrazides **3** and 2-amino-5-(3'-pentadecylaryloxyalkyl)-1,3,4-oxadiazoles **6** required as starting materials were prepared according to previously published methods [8, 9]: hydrazides **3** were condensed with various aromatic aldehydes **4** in the presence of ethanol medium to obtain benzal-3-pentadecylaryloxyalkyl carboxylic acid hydrazides **5a–r** (scheme 1). Similarly, oxa-

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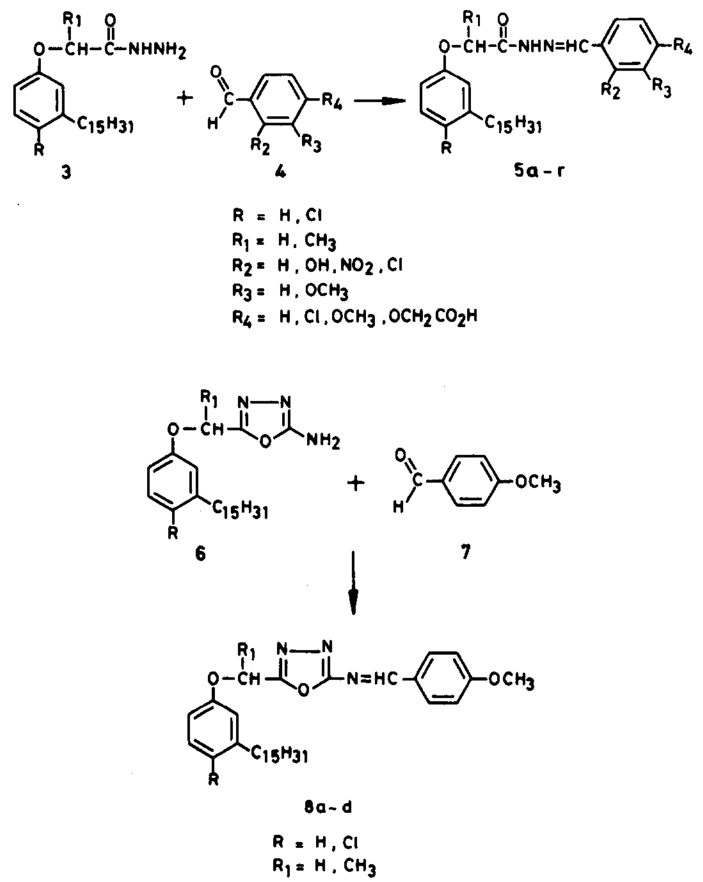

Scheme 1.

diazoles **6** were reacted with 4-methoxybenzaldehyde **7** in ethanol to obtain 2-(4'-methoxybenzalamino)-5-(3'-pentadecylaryloxyalkyl)-1,3,4-oxadiazoles **8a–d** (scheme 1). The structure of these compounds was confirmed by elemental analysis, IR, ^{1}H NMR and mass spectra. The synthesized compounds **5** and **8** together with their anti-inflammatory (antiedematous) activities are described in tables I and II respectively.

Results and Discussion

From the results summarized in tables I and II, it is apparent that the compounds **(5d, 5j, 5p)** possessing OCH_2CO_2H group in the benzal moiety showed promising anti-inflammatory (anti-edematous) activity (34, 36, 39%) respectively, in comparison to standard phenylbutazone (32%). Compounds **5f, 5g, 5k, 5q** (table I) and **8a–d** (table II) exhibited moderate anti-inflammatory (anti-edematous) activity (20–28%) in comparison to phenylbutazone, while others were less active.

Experimental protocols

Chemistry

Melting points were determined on a Büchi capillary melting point apparatus and are uncorrected. IR spectra were recorded on a Perkin–Elmer 283B spectrophotometer in a potassium bromide pellet. The NMR spectra were determined on a Jeol FX90Q FT NMR spectrometer using tetramethylsilane as an internal standard. Mass spectra were recorded on a VG 7070H mass spectrometer at 70 eV. The purity of all the compounds was verified by thin-layer chromatography.

*Benzal-3-pentadecylaryloxyalkyl carboxylic acid hydrazides **5a–r** (table I)*

General procedure. A mixture of 3-pentadecylaryloxyalkyl carboxylic acid hydrazide **3** (0.01 mol), corresponding aramatic aldehyde **4** (0.01 mol) and ethanol (50 ml) was refluxed on steam bath for 4 h. The solid mass obtained after cooling was filtered and recrystallized to obtain the respective title compound. Compound **5a** showed characteristic IR bands at 3 200 (NH), 1 670 (CO), 1 620 (C=N), 1 580 (aromatic), 1 250 (ether linkage), 2 920, 2 850 (alkyl stretching of $C_{15}H_{31}$) cm^{-1}; ^{1}H NMR (5m; $CDCl_3$) δ : 10.10 (br, 1H, NH); 8.22 (s, 1H, CH=); 6.75–7.76 (m, 9H, aromatic); 4.75 (q, 1H, CH–CH_3); 1.54 (d, 3H, CH–CH_3); 2.37–2.60 (t, 2H, CH_2); 1.22 [s, 26H, $(CH_2)_{13}$]; 0.71–0.95 (t, 3H, CH_3); MS: 5m, 478 (M$^+$).

*2-(4'-Methoxybenzalamino)-5-(3'-pentadecylaryloxyalkyl)-1,3,4-oxadiazoles **8a–d** (table II)*

General procedure. A mixture of 2-amino-5-(3'-pentadecyl-aryloxyalkyl)-1,3,4-oxadiazole **6** (0.005 mol) and 4-methoxy-benzaldehyde **7** (0.01 mol) was heated in an oil bath at 160–170°C for 2 h. The reaction product was cooled and triturated with petroleum ether to obtain the respective title compound. The product was recrystallized from methanol. Compound **8a** exhibited characteristic IR bands at 2 920, 2 850 (alkyl stretching of $C_{15}H_{31}$), 1 620 (C=N), 1 580 (aromatic), 1 240 (ether linkage) cm^{-1}, ^{1}H NMR (**8a**, $CDCl_3$) δ : 8.80 (s, 1H, CH=); 6.71–7.80 (m, 8H, aromatic); 4.85 (s, 2H, OCH_2); 3.61 (s, 3H, OCH_3); 2.40–2.61 (t, 2H, CH_2); 1.24 [s, 26H, $(CH_2)_{13}$]; 0.72–0.96 (t, 3H, CH_3); MS: 519 (M$^+$).

Anti-inflammatory (anti-edematous) activity: carrageenin-induced rat paw edema method

The experiment was performed according to Winter *et al* [10]. Male Wistar rats weighing 150–180 g were divided at random into groups of 5 animals and all the test compounds **5a–r** and **8a–d** were administered orally in 2% gum acacia suspension to the fasted rats at a dose of 100 mg/kg. 1 h later, 0.1 ml of 1% carrageenin was injected subcutaneously into the plantar surface of the right hind paw of each rat. After 2 h of the injection of carrageenin, the paw edema was measured plethysmographically. The percent inhibition of the edema of the treated rats with respect to controls was calculated and compared with phenylbutazone as the standard. The results are given in tables I and II.

Table I. Benzal-3-pentadecylaryloxyalkyl carboxylic acid hydrazides **5a–r**.

Compd	*R₂*	*R₃*	*R₄*	*mp (°C)*	*Yield (%)*	*Mol formula* [a]	*Anti-inflammatory action* [b] n [c]	*% inhibition of inflammation*
$R = R_1 = H$								
5a	H	H	H	104	94	$C_{30}H_{44}N_2O_2$	3	17
5b	OH	H	H	97	95	$C_{30}H_{44}N_2O_3$	3	15
5c	NO_2	H	H	85	96	$C_{30}H_{43}N_3O_4$	3	14
5d	H	H	OCH_2CO_2H	134	90	$C_{32}H_{46}N_2O_5$	8	34.10±3.25
5e	Cl	H	Cl	79–80	89	$C_{30}H_{42}Cl_2N_2O_2$	3	10
5f	H	OCH_3	OCH_3	95–96	93	$C_{32}H_{48}N_2O_4$	3	24
$R = Cl, R_1 = H$								
5g	H	H	H	105	89	$C_{30}H_{43}ClN_2O_2$	8	28±2.32
5h	OH	H	H	115	90	$C_{30}H_{43}ClN_2O_3$	3	14
5i	NO_2	H	H	109	88	$C_{30}H_{42}ClN_3O_4$	3	10
5j	H	H	OCH_2CO_2H	130	88	$C_{32}H_{45}ClN_2O_5$	8	36.56±3.85
5k	Cl	H	Cl	95–96	90	$C_{30}H_{41}Cl_3N_2O_2$	3	24
5l	H	OCH_3	OCH_3	75–76	87	$C_{32}H_{47}ClN_2O_4$	3	8
$R = H, R_1 = CH_3$								
5m	H	H	H	99	85	$C_{31}H_{46}N_2O_2$	3	17
5n	OH	H	H	96–97	85	$C_{31}H_{46}N_2O_3$	3	18
5o	NO_2	H	H	102	85	$C_{31}H_{45}N_3O_4$	3	9
5p	H	H	OCH_2CO_2H	150	84	$C_{33}H_{48}N_2O_5$	8	39.05±2.56
5q	Cl	H	Cl	100	82	$C_{31}H_{44}Cl_2N_2O_2$	3	24
5r	H	OCH_3	OCH_3	106	81	$C_{33}H_{50}N_2O_4$	3	10
Phenylbutazone							8	32.06±3.22

[a]All compounds were analyzed for C, H, N; the maximum deviation observed from the theoretical value was ± 0.4%.
[b]Dose: 100 mg/kg, *po*; *n*[c] = No of animals used.

Table II. 2-(4'-Methoxybenzalamino)-5-(3'-pentadecylaryloxyalkyl)-1,3,4-oxadiazoles **8a–d**.

Compd	*R*	*R₁*	*mp (°C)*	*Yield (%)*	*Mol formula* [a]	*Anti-inflammatory action* [b] n [c]	*% inhibition of inflammation*
8a	H	H	75–77	55	$C_{32}H_{45}N_3O_3$	3	20
8b	Cl	H	74–75	48	$C_{32}H_{44}ClN_3O_3$	3	22
8c	H	CH_3	83–85	51	$C_{33}H_{47}N_3O_3$	3	23
8d	Cl	CH_3	80–81	50	$C_{33}H_{46}ClN_3O_3$	8	28±2.10
Phenylbutazone						8	32.06±3.22

[a]All compounds were analyzed for C, H, N; the maximum deviation observed from the theoretical value was ± 0.4%.
[b]Dose: 100 mg/kg, *po*; *n*[c] = No of animals used.

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