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4-ACETAMIDOPHENAZONE DERIVATIVES

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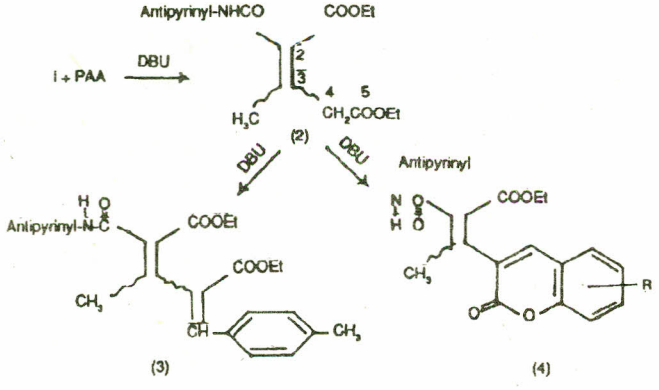
Condensation of ethoxycarbonylacetamidoantipyrine (1) with ethyl acetoacetate is described. The reactivity of methylene group in compound (2) toward different aromatic aldehydes is investigated. A series of 1,2,4-triazoles. and 1,3-thiazolidin-4-ones were synthesized. Oxazolinethione derivative was also prepared. The IR and 1H NMR of some selected compounds are reported.

Key words: Acetamidophenazone derivatives, Synthesis.

Introduction

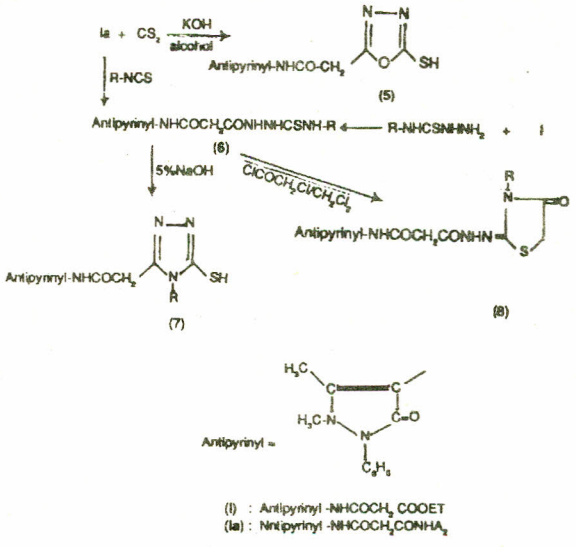
As a part of our studies directed towards the structural modifications of 4-aminoantipyrine [1-4] and in the course of our work on novel anti-inflammatory agents. It became of interest to investigate the extention of unsaturation (on the side chain situated at C-4 of the antipyrine [5]) and to introduce a groups of pharmacological interest.

The reaction of ethyl malonamidoantipyrine (1) with ethyl acetoacetate (EAA) in presence of DBU afforded the unsaturated ester (2). The assignment of the relative configuration of (2) was very difficult due to the absence of olefinic protons [6]. Compounds (3), (4a) and (4b) were obtained by reacting (2) with p-tolualdehyde, B-resorsaldehyde and B-naphthaldehyde respectively Scheme 1. On the other



SCHEME I

hand 1,3,4-oxadiazolin-5- thione (5) was prepared from the acylhydrazide of (1)[4] via reaction with carbon disulphide. The reaction of (1) with different thiosemicarbazides afforded compounds (6 a-d) which were also obtained through reaction of acylhydrazide derivative of (1) with the respective isothiocyanates. Cyclization of (6 a- c) in 5% NaOH solution gave 1,3,4-triazole derivatives (7 a-c). While reaction of (6 a,b) with chloroacetyl chloride afforded the corresponding 1,3-thiazoliden-4-one derivatives (8 a,b) Scheme 2.



SCHEME II

Experimental

I.R. studies were carried out on a Unicam SP 1000 spectrophotometer using (KBr) discs. 1H NMR were obtained with Varian EM. 390 and FT-200 spectrometer in $CDC1_3$ or DMSO-d_6 with TMS as internal standard. All m.ps were taken in open capillaries and are uncorrected.

Diethyl-3-methyl-2(4'-antipyrinylaminocarbonyl)-2-penten- 1,5-dioate (2) . A mixture of (1) (1 mmol), ethyl acetoacetate (1, 1mmol) and DBU (0.1 ml) was refluxed over an oil bath with continuous stirring during 15 minutes. Absolute ethyl alcohol (10 ml) was added and the reaction mixture was refluxed overnight. The solvent was then evaporated under reduced pressure and the residue dried by successive addition and evaporation of toluene and then was crystallized from methanol (Table 1). IR 3300 and 1640 cm^{-1} (NCHO), 1715 and 1730 cm^{-1} (two ester groups). 1H NMR ($CDC1_3$) o : 1.2-1.5 (two t, 6H, two O-CH_2CH_3), 1.8 (s, 3H, = C- CH_3 lateral chain), 2.2(s, 3H, =C-CH_3), 3.2 (s, 3H, -NCH_3) 3.1 (s, 2H, = C-CH_2COOEt), 3.9-4.3 (two q, 4H, -OCH_2CH_3) 5-3(s, 1H, NHCO, exchangeable with D_2O) and 7-1-7.4 (m, 5H, Ar-H).

Diethyl-3-methyl-2-(4' antipyrinylaminocarbonyl)-4-(p-

Table 1. Yield, Melting Point and Elemental analysis of compound 2-8b.

No.	R	Yield (%)	Crystallisation solvent	Molecular formula	Analysis (%) Calc./Found C	H	N	MP
(2)		60	Methanol	$C_{22}H_{27}N_3O_6$	61.54 61.40	6.29 5.90	9.79 9.80	155-156.5
(3)	p-CH_3-C_6H_5	65	Ethanol 95%	$C_{30}H_{33}N_3O_6$	67.80 67.60	6.21 6.50	7.91 8.00	207.5-208.5
(4a)	7-hydroxy	74	DMF	$C_{27}H_{25}N_3O_7$	64.41 64.20	4.97 4.70	8.35 -	299-300
(4b)	5,6-e benzo	57	Ethanol 95%	$C_{31}H_{27}N_3O_6$	69.27 69.20	5.03 5.40	7.82 7.80	282-283
(5)	-	56	DMF/water	$C_{15}H_{15}N_5O_3S$	52.17 52.00	4.35 4.50	20.29 20.29	224-225
(6a)	n-C_4H_5	65[a]	Ethanol 95%	$C_{19}h_{26}N_6O_3S$	54.53 54.70	6.26 6.20	20.08 19.80	204-206
(6b)	C_6H_5	61[a] 50[b]	"	$C_{21}H_{22}N_6O_3S$	57.52 57.70	5.06 5.20	19.17 19.10	183-185
(6c)	$C_6H_5CH_2$	54[b]	"	$C_{22}H_{24}N_6O_3S$	58.39 58.70	5.35 5.40	18.57 -	114-115
(6d)	o-OCH_3-C_6H_4	51[b]	"	$C_{22}H_{24}N_6O_4S$	56.40 56.30	5.16 5.30	17.94 18.10	140-142
(7a)	n-C_4H_9	43	"	$C_{19}H_{24}N_6O_2S$	56.98 57.30	6.04 5.80	20.98 21.30	167-270
(7b)	C_6H_5	47	DMF/ethanol	$C_{21}H_{20}N_6O_2S$	59.99 60.20	4.79 4.70	19.99 20.20	297-300
(7c)	$C_6H_5CH_2$	45	Ethanol/water	$C_{22}H_{22}N_6O_2S$	60.81 60.60	5.10 5.20	19.34 19.10	152-155
(8a)	n-C_4H_9	75	"	$C_{21}H_{26}N_6O_4$	55.01 55.10	5.72 5.50	18.41 -	216-218
(8b)	C_6H_5	67	Ethanol	$C_{23}H_{22}N_6O_4S$	57.73 57.50	4.63 4.60	16.74 16.50	222-225

methylbenzylidene)-2-penten-1,5-dioate (3) : A mixture of (2) (1mmol), p-tolualdehyde (1.0 1mmol) and DBU (0.1 ml) was treated as above to give (3) (Table 1).

Ethyl-2-(4'-antipyrinylaminocarbonyl)-3-3"(7"-hydroxy and (5",6"-e benzo) counmarinyl-2-butenoate (4a and 4b) respectively): A mixture of (2) (1mmol), B-resorsylaldehyde or 2- hydroxy-1-naphthaldehyde (1.1mmol) and DBU (0.1 ml) was treated as above to give 4a and 4b respectively (Table 1). 1R of compound (3) and (4)1632 cm^{-1} (C=C-C=C) and 1740 cm^{-1} (cyclic lactone). IH NMR compound 4a (DMSO-d_6) O : 8.2 (s, 1H, Hc-4-coumarin), 9.1 (s, 1H, CONH; D_2O exchanged) and 6.9 (s, 1H, OH; D_2O exchanged).

2-(4'-antipyrinylaminoacetyl)-5-mercapto-1,3,4-oxadiazole (5): Carbon disulphide (2.5 ml) was added to a solution of (1a) (10 mmol); KOH (10 mmol) in water (2 ml), ethanol (40 ml) and the mixture was refluxed for 10 hours. The solvent was then distilled off, the obtained residue was dissolved in water (50 ml), filtered and the filtrate was acidified with dil. HCl, the precipitate was filtered off, washed with cold water, dried and crystallized (Table 1).

N^1-(4'-antipyrinylaminoacetyl)-N^4-substituted thiosemicarbazides (6 a-b). Method a. (1 a) (10 mmol) was suspended in ether (50 ml) then and equivalent amount of the appropriate isothiocyanate in ethanol (20 ml) was added while heating over a water bath. The obtained clear solution was refluxed for 1 hrs. and then allowed to cool. The separated slurry was then crystallised (Table 1).

Method b: A mixture of (1) (10 mmol) and the appropriate substituted thiosemicarbazone (10 mmol) in ethanol (70 ml) was refluxed during two hrs. and the reaction mixture was then concentrated. The crude product separated on cooling was then crystallised (Table 1).

3-(4'-antipyrinylaminoacetyl)-4-substituted-5-mercapto- 1,2,4-triazoles (7a-c): A solution of (6a-c) (10 mmol) in 5% NaOH (50 ml) was refluxed for 1 hr. and then filtered while hot. The pH of the filterate was adjusted between 5-6 by addition of dil. HCl and the separated solid was filtered, washed with water, dried and finally crystallised (Table 1).

2-(4'-antipyrinylcarbonylacetylhydrazono)-3-substituted-4-oxo-1,3-thiazolidenes (IX a and b): A solution of respective (6a,b) (lmmol) in CH_2C1_2 (15 ml) was treated with an equivalent of chloroacetylchloride and the reaction mixture was then refluxed for 10 hrs. The reaction mixture was then concentrated and the separated solid was filtered and crystallised (Table 1). ^{1}H NMR Compound (8a) (DMSO-d_6): o 4 and 4.3 (25, 4H, $COCH_2CO$ and cyclic- s-CH_2-CO-).

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