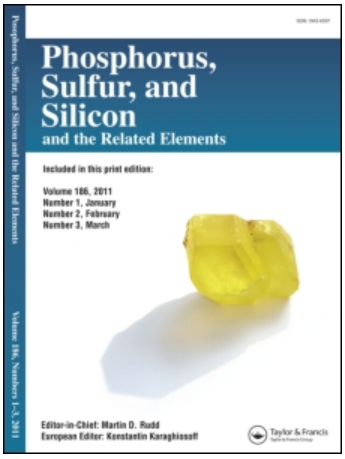

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REACTIONS OF 4-ISOTHIOCYANATO-4-METHYL-2-PENTANONE WITH AMINES HAVING FUNCTIONAL GROUP AT β POSITION AND ANTI-INFLAMMATORY EVALUATION OF RESULTING HETEROCYCLIC COMPOUNDS

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REACTIONS OF 4-ISOTHIOCYANATO-4-METHYL-2-PENTANONE WITH AMINES HAVING FUNCTIONAL GROUP AT β POSITION AND ANTI-INFLAMMATORY EVALUATION OF RESULTING HETEROCYCLIC COMPOUNDS

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The reaction of 4-isothiocyanato-4-methyl-2-pentanone with *o*-phenylenediamine at room temperature yielded isomeric mixture of 1-(2'-aminophenyl)-4,4,6-trimethyl-1,4,5,6-tetrahydro-6-hydroxypyrimidine-2(3H)-thione (**I**), which on refluxing in MeOH with catalytic amount of sulphuric acid cyclizes to yield the known pyrimidobenzimidazole (**IIa**). The same product was also obtained by direct condensation of *o*-phenylenediamine with 4-isothiocyanato-4-methyl-2-pentanone in the presence of catalytic amount of acid and heating under reflux for 8 h. The reaction of 4-nitro-1,2-phenylenediamine with 4-isothiocyanato-4-methyl-2-pentanone gave **IIb**. The reaction of *o*-aminophenol with 4-isothiocyanato-4-methyl-2-pentanone at pH 4.3 gave 1-(2'-hydroxyphenyl)-4,4,6-trimethyl-1,4-dihydro-pyrimidine-2(3H) thione (**III**), however the same reaction under strongly acidic conditions (pH ~ 1) gave the known pyrimidobenzoxazole (**IV**). The reaction of 4-isothiocyanato-4-methyl-2-pentanone with *o*-aminothiophenol and 2-amino ethanol under different pH conditions gave the known heterocycles **V** and **VI**, respectively. The structures of these compounds are supported by IR, ^{1}H NMR and HRMS. Anti-inflammatory evaluation of **I**, **IIa**, **IIb**, **III**, **IV**, **V** and **VI** at 100 mg/kg showed that compounds **I**, **IIa**, **III**, and **IV** are inactive whereas, compounds **IIb**, **V** and **VI** showed 13%, 11%, and 21% activity, respectively.

Key words: Isothiocyanato pentanone; amines; heterocyclic; anti-inflammatory activity; NMR; HRMS.

INTRODUCTION

Aspirin, phenylbutazone, oxyphenbutazone, indomethacin, ibuprofen, ketoprofen, etc., form a group of nonsteroidal anti-inflammatory analgesic drugs used for the symptomatic relief from the symptoms of inflammation.[1] These drugs have ulcerogenic activity as a side effect. A comparative study[2] has been reported on gastrointestinal lesions caused by common anti-inflammatory drugs and it has been reported that the order of potency causing blood loss was indomethacin >> ibuprofen > aspirin > oxaprozin. Pyrazolo[1,5-a]pyrimidine,[3] 1-benzyl benzimidazole[4] and pyrimidobenzimidazole derivatives[5,6] have been reported in the literature as modifying anti-rheumatic and gastric acid secretion inhibitors. The volume of literature published in this area every year indicates the need for the synthesis and

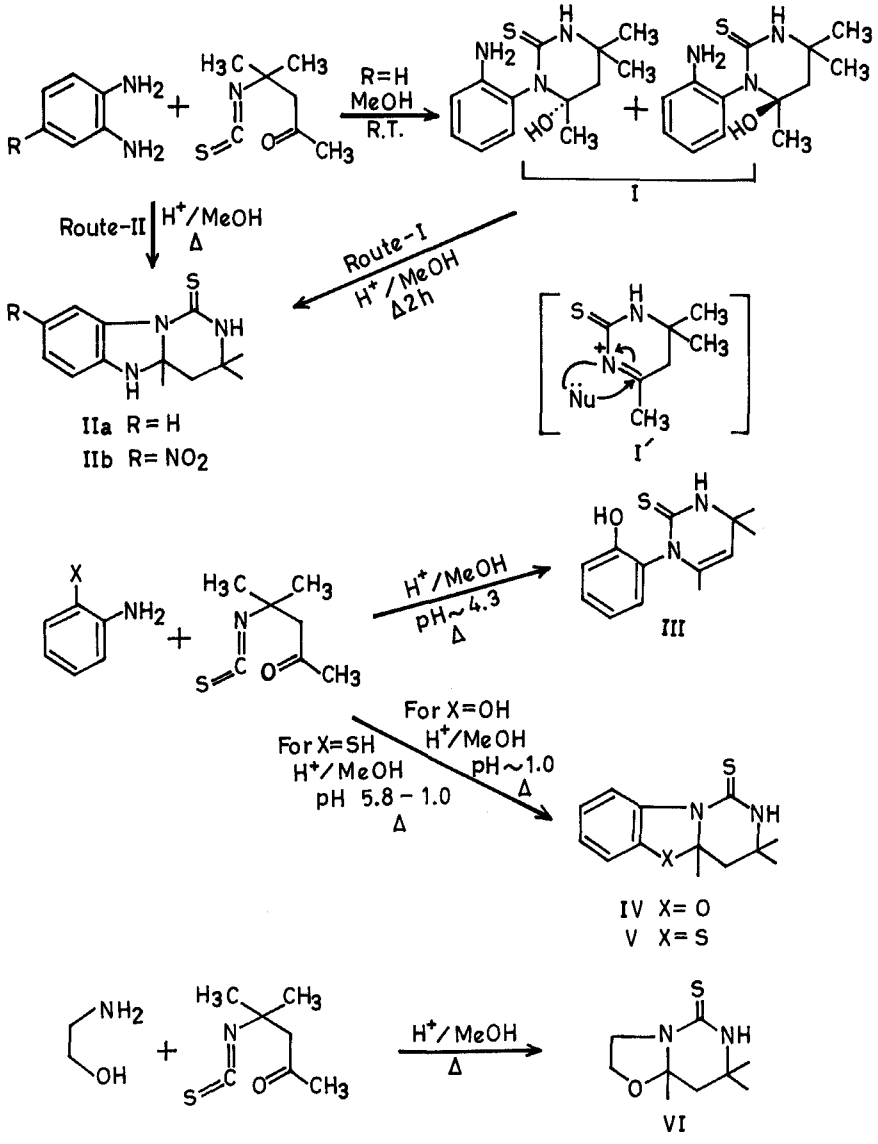
development of safer anti-inflammatory drugs. In continuation of our efforts towards this direction[7–9] we wish to report the synthesis and anti-inflammatory evaluation of some S & N containing heterocyclic compounds.

RESULTS AND DISCUSSION

The reactions of 4-isothiocyanato butan-2-one, 3-isothiocyanato butanal and 4-isothiocyanato-4-methyl-2-pentanone with amines having functional group at β or γ position have been reported at reflux temperature of toluene or xylene[10] and also under basic conditions.[11] We have studied the reaction of 4-isothiocyanato-4-methyl-2-pentanone with *o*-phenylenediamine, 4-nitro-1,2-phenylenediamine, *o*-amine phenol, *o*-amino-thiophenol, and 2-amino ethanol at room temperature/ under acidic conditions and in some cases different reaction products were obtained depending on the reaction conditions used.

The reaction of *o*-phenylenediamine with 4-isothiocyanato-4-methyl-2-pentanone in MeOH at room temperature yielded 1-(2′-aminophenyl)-4,4,6-trimethyl-1,4,5,6-tetrahydro-6-hydroxy-pyrimidine-2(3H)thione (**I**). The ^{1}H NMR (300 MH$_z$; DMSO-d_6) show two sets of peaks for —NH_2 (s; 4.60; 3/2H, and s; 4.90; 1/2H), —OH (s; 5.75; 3/4H, and s; 5.95; 1/4H), and —NH— (s; 8.38; 3/4H, and s; 8.45; 1/4H). This observation indicates that **I** is a mixture of isomers. Existence of various isomers in case of **I** is possible due to restricted rotation of both the rings and due to asymmetric carbon atom C_6. When ^{1}H NMR spectrum was run at 60°C the two singlets at δ 8.38 and 8.45 (due to N—Hs) merged to a singlet due to rapid intermolecular proton exchange processes. From the presence of two sets of peak due to —NH_2 and —OH even at 60°, it is concluded that at 60°C there still exist two rotational isomers. HRMS of **I** gave M^+ ion peak at 265.1255 (M^+, 30%) Calc. for $C_{13}H_{19}N_3SO$ 265.1251.

The product **I** was also obtained by alternative route as reported earlier.[12] When compound **I** was heated under reflux for 2 h in methanol using catalytic amount of sulphuric acid, the known cyclized product **IIa** was obtained in good yield. The same product **IIa** was also obtained by refluxing *o*-phenylenediamine and 4-isothiocyanato-4-methyl-2-pentanone in methanol under acidic conditions. The structure of **IIa** is supported by correct IR, ^{1}H NMR and HRMS. The signals at δ 4.60 and 4.90 and 5.75 and 5.95 (due to —NH_2 and —OH) were absent in the ^{1}H NMR of **IIa** indicating cyclization of **I** to **IIa**. The ^{1}H NMR of **IIa** did not show any doubling of signals, again indicating cyclization of **I** to **IIa**. The pyrimidobenzimidazole (**IIa**) obtained by both the routes was the same as confirmed by superimposable ^{1}H NMR, IR and undepressed mix mp. HRMS of **IIa** gave M^+ ion peak at 247.1148 (Calc. for $C_{13}H_{17}N_3S$ 247.1143), further confirming the structure of **IIa**. When 4-nitro-1,2-phenylenediamine was condensed with 4-isothiocyanato-4-methyl-2-pentanone under acidic conditions pyrimidobenzimidazole **IIb** was obtained in 70% yield. The structure of **IIb** is supported by IR, ^{1}H NMR and HRMS. The ^{1}H NMR data clearly show that the proton at lowest field (9.5 ppm deshielded by the near by C=S function) is a singlet (no coupling to an ortho proton). This rules out the isomeric structure with the nitro group in meta position to the benzimidazole NH function. Thus the view is confirmed that the substantially



SCHEME I

more nucleophilic —NH_2 group situated meta to the NO_2 group reacts first with isothiocyanate function.

The reaction of *o*-aminophenol with 4-isothiocyanato-4-methyl-2-pentanone at pH 4.3 gave 1-(2′-hydroxyphenyl)-4,4,6-trimethyl-1,4-dihydro-pyrimidine-2(3H)-thione (**III**). The ^{1}H NMR spectrum of **III** shows a singlet at δ 4.80 corresponding to —CH=C— and CIMS shows MH^+ ion peak at 249 (100%) confirming the structure of **III**. However, when the same reaction was done at pH ~ 1.0 the known pyrimidobenzoxazole (**IV**) was obtained. The structure of **IV** is supported by correct ^{1}H NMR, IR and HRMS. The ^{1}H NMR of **IV** shows a doublet at δ 2.2 and another

doublet at 2.60 accounting for one proton each and having geminal coupling constant 18 Hz, indicating the presence of —CH_2— group of the pyrimidine ring. HRMS of **IV** shows M^+ ion peak at 248.0993 Calc. for $C_{13}H_{16}N_2SO$ 248.10027. When the reaction of *o*-aminothiophenol was carried out at pH ranging from 5.8–1, unlike *o*-aminophenol (where two products were obtained), only one, the known pyrimidobenzothiazole (**V**), was obtained. The structure of **V** is again supported by correct ^1H NMR, HRMS and IR spectra. The ^1H NMR of **V** shows a doublet at δ 2.50 and another doublet at 2.65 each accounting for one proton. These two doublets belong to —CH_2— group of pyrimidine ring.

The reaction of 2-amino ethanol with 4-isothiocyanato-4-methyl-2-pentanone at pH ~ 2 was carried out and the product obtained was the well known oxazolopyrimidinethione (**VI**). The structure of compound **VI** is supported by correct ^1H NMR, IR and HRMS.

TABLE I

Physical constants of various compounds

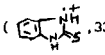
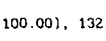
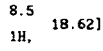
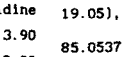
Compd. No. 1	Solvent of Cryst 2	mp °C 3	Yield % 4	IR(ν_{max})cm^{-1} selected band 5	^1H NMR (300 MHz, DMSO-d_6) δppm 6	Mass Spectral data m/z (rel. Int.) 7
I	THF	255	75	3303(-NH_2,-OH) 1647 & 1540 (Ar)	1.15(overlapping doublets, 6H, 2xCH_3),1.45(s,3H,CH_3), 1.95(d, 1H, Jgem=15Hz,one H of-CH_2-),2.05(d,1H,Jgem =15Hz, one H of -CH_2-), 4.60(s,3/2 H, -NH_2 exch), 4.90(s, 1/2 H,-NH_2 exch), 5.75(s, 3/4 H,-OH exch), 5.95(s, 1/4 H,-OH, exch), 6.5(q, 1H, Ar), 6.60(m, 1H, Ar),7.00(m, 2H, Ar), 8.38(s, 3/4 H, -NH-exch), 8.45(s, 1/4 H -NH- exch).	265.1255(M^+,30) calcd for $C_{13}H_{19}N_3SO$ 265.1251, 247.1147(M^+-H_2O, 13.84), 232.1450(M^+- SH, 26.56), 232.0910 (247.1147 -CH_3, 16.25), 214.1345(M^+-(H_2O +SH, 6.10), 150.0253 ( ,33.79),108.0687 ($C_6H_8N_2$, 100.00), 92.0500 (150.0253 -NCS, 14.63).
IIa	THF	223 Lit. 230-232	86	3200 (-NH-)	1.2(d, 6H, CH_3+CH_3), 1.35 (s, 3H,-CH_3), 2.10(s, 1H, Jgem=15Hz), 2.32(d, 1H , Jgem=15Hz), 6.5 (m, 3H, one H exch. -NH + 2H Ar), 6.80(t, 1H, Ar), 8.3 (s, -C-NH, exch), 8.55(d, 1H, (Ar).	247.1148(M^+, 51.84) calcd for $C_{13}H_{17}N_3S$ 247.1143, 232.0908(M^+-CH_3 , 66.17), 173.1080(232.0908 -HSCN , 100.00), 132.0687( 76.90)131.0617(132.0687-H, 19.62),91.0435(C_6H_5N,3.23)
IIb	THF	260	79	3250 (-NH -) 1630 (Ar).	1.25(d, 6H, CH_3 +CH_3), 1.50(s, 3H, CH_3), 2.20(d, 1H, Jgem=18Hz), 2.55(d, 1H, Jgem=18Hz), 6.50(d, 1H, Ar), 7.90(d, 1H, Ar), 8.30(s, 1H, -NH- exch) , 8.80(s, 1H, -C-NH-,exch), 9.50(s, 1H, Ar)	292.0990(M^+,68.24), calcd for $C_{13}H_{16}N_4SO_2$ 292.09866 277.0759[M^+ -CH_3, 76.84), 218.0930[M^+ -(CH +HSCN) , 100.00], 178.0609( 37.93),177.0538(178.0609-H, 55.78), 172.0999(218.0930 -NO_2, 43.75) , 131.0610 (177.0538 - NO_2, 26.08), 100.022[$(CH_3)_2$CNCS,20.53]

TABLE I (*Continued*)

1	2	3	4	5	6	7
III	MeOH : H_2O	190	40	3194(-NH-,-OH), 1694(C=C), 1533 (Ar)	1.2(d, 6H, CH_3+CH_3), 1.40 (s, 3H, CH_3), 4.80(s, 1H, -CH=C-), 6.70(t, 1H, Ar), 6.80(d, 1H, Ar), 7.0(d, 1H, Ar), 7.10(t, 1H, Ar), 8.65(s, 1H, -NH- exch).	CIMS. 249(MH^+, 100%).
IV	MeOH : H_2O	178 Lit. 178	50	3215 (-NH-)	1.25(2s,6H, CH_3+CH_3),1.50 (s, 3H,-CH_3), 2.2(d, 1H, Jgem=18Hz), 2.60 (d , 1H, Jgem=18Hz), 6.80(m, 2H, Ar), 7.0(m, 1H, Ar), 8.5 (m, 1H, Ar), 8.80(s, 1H, -NH- exch).	248.0993(M^+, 60.74), calcd. for $C_{13}H_{16}N_2SO$ 248.10027, 233.0754 (M^+-CH_3, 11.00),215.1187(M^+-SH, 4.53),174.0920[M^+- (CH+HSCAN) , 18.62], 134.0611( 100.00), 133.0533(134.0611 -H , 20.96),100.0222(Me_2CNCS, 20.54)
V	MeOH	172 Lit. 173-175	52	3172 (-NH-) 1532(Ar)	1.35(s, 6H,CH_3+CH_3), 1.73 (s, 3H, CH_3), 2.50(d,1H), 2.65(d, 1H,), 7.05(m, 2H, Ar), 7.30(m, 1H, Ar), 8.55(d, 1H, Ar), 9.0(s, 1H, -NH, exch).	264.0752(M^+, 98.95), calcd. for $C_{13}H_{16}N_2S_2$ 264.0750, 249.0520 (M^+-CH_3, 36.97), 231.0953(M^+ -SH, 12.85], 190.6900[M^+-(CH_3 + HSCN),52.55],150.0372( 100.00), 149.0275(150.0372 -H , 50.07),100.0220 (Me_2CNCS,10.38),
VI	MeOH	176 Lit. 184	55	3219 (-NH -)	1.2(d, 6H, CH_3 +CH_3) , 1.40(s, 3H, CH_3), 1.70(d, 1H, Jgem = 15Hz one H of -CH_2-of pyrimidine ring), 2.20(d, 1H, Jgem=15Hz one H of -CH_2- of pyrimidine ring), 3.60(m. 1H), 3.90 (m, 2H), 4.15(m, 1H),8.30 (s, 1H, -NH-, exch).	200.0984(M^+ , 100.00), calcd. for $C_9H_{16}N_2SO$ 200.0985.185.0749 (M^+ -CH_3,47.52),167.1182(M^+-SH, 1.39), 126.0920[M^+ -(CH_3+HSCN), 46.07] , 100.0220 (Me_2CNCS, 19.05), 86.0615( 32.23), 85.0537 (86.0615 -H, 10.03).

In all these reactions the formation of **IIa**, **b**, **IV**, **V** and **VI**, under acidic conditions can be explained by assuming that first an immonium salt I′ is formed which is attacked by the internal nucleophile to give the final products. The physical constants and spectral data of **I**, **IIa**, **IIb** and **III–VI** are reported in Table I.

Compounds **I**, **IIa**, **IIb**, **III–VI** were tested for anti-inflammatory activity at 100 mg/kg. Compounds **I**, **IIa**, **III**, and **IV** were inactive and compounds **IIb**, **V** and **VI** showed 13%, 11% and 21% activity, respectively.

EXPERIMENTAL

Melting points, determined on a JSGW apparatus are uncorrected. Only principal sharply defined IR peaks are reported. ^{1}H NMR spectra were recorded on approximately 5–15% (W/V) solutions in appropriate deuterated solvents with tetramethyl silane as internal standard. Line positions are recorded in ppm from the reference. The MS spectrometer peak measurements were made by comparison with perfluorotributylamine at a resolving power of 15,000. TLC was performed by using silica gel G for TLC (Merck) and spots were visualized by iodine vapour or by irradiation with U.V. light 254 nm.

Synthesis of 1-(2'-aminophenyl)-4,4,6-trimethyl-1,4,5,6-tetrahydro-6-hydroxy-pyrimidine-2(3H)thione (**I**):

(i) *o*-Phenylenediamine (2.16 g, 0.02 mol) was dissolved in methanol (20 ml) and to it was added 4-isothiocyanato-4-methyl-2-pentanone (3.50 g, 0.022 mol). The reaction mixture was stirred at room temperature for 1 h and then kept at room temperature for 24 h. The white solid separated out which was filtered, washed with cold methanol and air dried. The crude product was crystallized from THF to give 1-(2'-aminophenyl)-4,4,6-trimethyl-1,4,5,6-tetrahydro-6-hydroxy-pyrimidine-2(3H)-thione (**I**).

Synthesis of pyrimidobenzimidazole **IIa** *(R=H).* 1-(2'-Aminophenyl)-4,4,6-trimethyl-1,4,5,6-tetrahydro-6-hydroxy-pyrimidine-2(3H)-thione (**I**) (530 mg, 0.002 mol) was dissolved in methanol (20 ml) and to it was added 2 drops of conc. sulphuric acid (pH ~ 2.3). The reaction contents were heated under reflux for 2 h. Solvent was removed under reduced pressure and to the residue left behind was added sodium carbonate solution and solid so obtained was filtered, washed thoroughly with water and air dried. The crude product was recrystallized from THF. Yield 330 mg (67%).

(ii) *o*-Phenylenediamine (2.16 g, 0.02 mol) was dissolved in methanol (20 ml) and to it was added 4-methyl-4-isothiocyanato-2-pentanone (3.50 g, 0.022 mol) and 2 drops of conc. sulphuric acid (pH ~ 6.0). The reaction contents were heated under reflux for 8 h. Solvent was removed under reduced pressure and the residue left behind was basified with sodium carbonate solution. Solid so obtained was filtered, washed with water and air dried. The crude product was recrystallized from THF. The products obtained via route (i) and (ii) gave undepressed mix m.p., superimposable IR, and ^{1}H NMR spectra indicating that same product (**IIa**) was obtained from both the routes.

Reaction of 4-nitro-1,2-phenylenediamine with 4-isothiocyanato-4-methyl-2-pentanone. (**IIb**, R=NO_2). 4-Nitro-1,2-phenylenediamine (1.0 g, 6.6 mmol) was suspended in methanol (40 ml) and to it was added 4-isothiocyanato-4-methyl-2-pentanone (1.09 g 7.0 mmol) and conc. sulphuric acid (0.17 ml, 3.3 mmol). The reaction contents were heated under reflux for 8 h and then cooled in an ice bath. The solid so separated was filtered, washed with sodium carbonate solution and then with water and air dried. The crude product so obtained was recrystallized from THF.

Synthesis of 1-(2'-hydroxyphenyl)-4,4,6-trimethyl-1,4-dihydropyrimidine-2(3H)-thione (**III**). *o*-Aminophenol (2.18 g, 0.02 mol) was dissolved in methanol (30 ml) and to it was added 4-isothiocyanato-4-methyl-2-pentanone (3.50 g, 0.025 mol) and 2 drops of conc. sulphuric acid (pH ~ 4.3). The reaction mixture was heated under reflux for 8 h. Solvent was removed under reduced pressure and the residue left behind was basified with sodium carbonate solution. Solid so obtained was washed with water and air dried. The crude product was recrystallized from aqueous methanol.

Synthesis of pyrimidobenzoxazole (**IV**). *o*-Aminophenol (2.18 g, 0.02 mol) was dissolved in methanol (30 ml) and to it was added 4-isothiocyanato-4-methyl-2-pentanone (3.45 g, 0.022 mol) and conc. sulphuric acid (1 ml). The reaction contents were heated under reflux for 6 h. Solvent was removed under reduced pressure and the residue left behind was basified with sodium carbonate solution. The solid so obtained was filtered, washed with water and air dried. The crude product was recrystallized from aqueous methanol.

Synthesis of pyrimidobenzthiazole (**V**). *o*-Aminothiophenol (2.50 g, 0.02 mol) was taken in methanol (30 ml) and to it was added 4-isothiocyanato-4-methyl-2-pentanone and conc. sulphuric acid (1 ml). The reaction contents were heated under reflux for 6 h. Solvent was removed under reduced pressure and the residue left behind was basified with sodium carbonate solution. The solid so obtained was filtered, washed with water and air dried. The crude product so obtained was crystallized from methanol.

Synthesis of pyrimidooxazole (**VI**). 2-Aminoethanol (3.5 g; 0.05 mol) was taken in methanol (20 ml) and to it was added 4-isothiocyanato-4-methyl-2-pentanone (7.8 g, 0.05 mol) and conc. sulphuric acid (2.7 ml; 0.05 mol). The reaction contents were heated under reflux for 8 h. Solvent was removed under reduced pressure and the residue left behind was basified by sodium carbonate solution. The solid so obtained was filtered, washed with water and air dried. The crude product was recrystallized from methanol.

Anti-inflammatory activity testing.[13] Anti-inflammatory activity testing was carried out by using carrageenin-induced oedema in albino rats: The oedema in one of the hind paws was induced by injection of 0.1 ml of 1% carrageenin solution into planter aponeurosis. The volume of the paw was measured plethysmo-graphically immediately after and 3 h after the injection of the irritant. The difference in volume gave the amount of oedema developed. Percent inhibition of the oedema between the control group and the compound treated group was calculated and compared with the group receiving standard drug. At 100 mg/kg p.o. none of the compounds possessed potent anti-inflammatory activity. However,

compounds **IIb**, **V** and **VI** inhibited the carrageenin induced hind paw oedema by 13, 11 and 21%, respectively, as compared to the standard drug, phenylbutazone which showed 35% activity at 30 mg/kg p.o. The activity shown by compound **VI** seems to be encouraging and further chemical manipulation could lead to a promising anti-inflammatory compound.

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