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Note

Synthesis of 5-arylidene-2-aryl-3-(phenothiazino/benzotriazoloacetamidyl)-1,3-thiazolidine-4-ones as antiinflammatory, anticonvulsant, analgesic and antimicrobial agents

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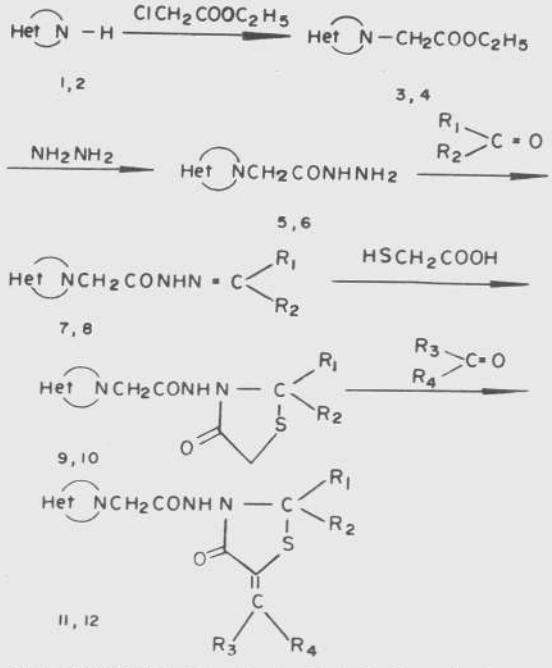
Condensation of N^{10}(acetohydrazido) phenothiazine/benzotriazole **5**, **6** with various carbonyls give arylidene acetohydrazido phenothiazines/benzotriazoles **7**, **8** which on cycloaddition with mercapto acetic acid yield the corresponding 4-thiazolidinones **9a-e** and **10a-e**. Treatment of these 4-thiazolidinones with various carbonyl compounds afford 5-arylidene-2-aryl-3-(phenothiazino/benzotriazolo acetamidyl)-1,3-thiazolidine-4-ones **11a-l** and **12a-l** respectively.

Phenothiazine and benzotriazole derivatives possess potent biological activities[1,2] including anthelmintic and antiinflammatory activities. 4-Thiazolidinones are well known for versatile pharmacological activities[3-5] such as hypnotic, anaesthetic, antifungal, analgesic, antiviral, antithyroid, anticonvulsant, CNS stimulant, etc.

The present paper reports the synthesis of 4-thiazolidinones by appropriate methods. All the compounds have been screened for their antiinflammatory activity against the carrageenan induced rat paw oedema in albino rats, anticonvulsant activity against pentylenetetrazole induced convulsions in mice, analgesic activity by the Eddy and Leimbach method using Technoheated plate analgesic apparatus and antimicrobial activity by the agar plate diffusion technique.

Phenothiazine/benzotriazole on N-esterification with ethyl chloroacetate in acetone/chloroform gave ethyl ethanoate/phenothiazine/benzotriazole **3**, **4** which on ammonolysis with hydrazine hydrate in ethanol/methanol yielded acetohydrazido phenothiazine/benzotriazole **5**, **6**. Compounds **5**, **6** on condensation with various carbonyls afforded arylidene acetohydrazido phenothiazine/benzotriazole **7**, **8** which on cyclocondensation with thioglycolic acid in presence of anhyd. $ZnCl_2$ furnished 2-aryl-3- (phenothiazino/benzotriazolo acetamidyl)-1,3-thiazolidene-4-ones **9**, **10**. Compounds **9**, **10** on reaction with various carbonyls using sodium ethoxide in dioxane/benzene yielded 5-arylidene-2-aryl-3-(phenothiazino/benzotriazolo acetamidyl)-1,3-thiazolidine-4-ones **11**, **12** (Scheme I).



Het = Phenothiazine in 1, 3, 5, 7, 9 and 11
Het = Benzotriazole in 2, 4, 6, 8, 10 and 12
R_1, R_2, R_3, R_4 = H /aryl/ sub. aryl

Scheme I

The structures of these compounds were established on the basis of their elemental analysis, IR, PMR and mass spectra (Table I).

Biological activities

Antiinflammatory activity

Carrageenan induced rat paw oedema method was employed for evaluating the antiinflammatory activity of **11 a-l** and **12 a-l** at a dose of 4 mg/kg b.w. in

Table I—Characterization data of compounds **7-12**

Compd	R_1	R_2	R_3	R_4	Yield (%)	m.p. (°C)	Mol. formula	Found(%) (Calcd) C	H	N
7b	H	CH=CH.C_6H_5	-	-	57	138	$C_{23}H_{19}N_3OS$	71.6 (71.6)	4.8 (4.9)	10.8 (10.9)
c	H	*p*-Cl.C_6H_4	-	-	61	93	$C_{21}H_{16}N_3OSCl$	64.0 (64.0)	3.9 (4.0)	10.5 (10.6)
d	H	*o*-Cl.C_6H_4	-	-	63	91	$C_{21}H_{16}N_3OSCl$	64.0 (64.0)	4.0 (4.0)	10.5 (10.6)
e	C_6H_5	C_6H_5	-	-	66	178	$C_{27}H_{21}N_3OS$	74.4 (74.4)	4.7 (4.8)	9.6 (9.6)
8b	H	CH=CH.C_6H_5	-	-	54	82	$C_{17}H_{15}N_5O$	66.7 (66.8)	4.9 (4.9)	22.9 (22.9)
c	H	*p*-Cl.C_6H_5	-	-	55	79	$C_{15}H_{12}N_5OCl$	57.3 (57.4)	3.7 (3.8)	22.3 (22.3)
d	H	*o*-Cl.C_6H_4	-	-	55	77	$C_{15}H_{12}N_5OCl$	57.3 (57.4)	3.7 (3.8)	22.3 (22.3)
e	C_6H_5	C_6H_5	-	-	56	67	$C_{21}H_{17}N_5O$	70.9 (70.9)	4.7 (4.7)	19.6 (19.7)
9b	H	CH=CH.C_6H_5	-	-	64	142	$C_{25}H_{21}N_3O_2S_2$	65.2 (65.3)	4.3 (4.5)	9.1 (9.1)
c	H	*p*-Cl.C_6H_4	-	-	47	89	$C_{23}H_{18}N_3O_2S_2Cl$	59.0 (59.0)	3.7 (3.8)	8.8 (8.9)
d	H	*o*-Cl.C_6H_4	-	-	50	87	$C_{23}H_{18}N_3O_2S_2Cl$	59.0 (59.0)	3.7 (3.8)	8.9 (8.9)
e	C_6H_5	C_6H_5	-	-	47	173	$C_{29}H_{23}N_3O_2S_2$	68.1 (68.3)	4.4 (4.5)	8.1 (8.2)
10b	H	CH=CH.C_6H_5	-	-	71	90	$C_{19}H_{17}N_5O_2S$	60.0 (60.1)	4.2 (4.4)	18.4 (18.4)
c	H	*p*-Cl.C_6H_4	-	-	65	74	$C_{17}H_{14}N_5O_2SCl$	52.5 (52.6)	3.5 (3.6)	18.0 (18.0)
d	H	*o*-Cl.C_6H_4	-	-	69	72	$C_{17}H_{14}N_5O_2SCl$	52.6 (52.6)	3.5 (3.6)	18.0 (18.0)
e	C_6H_5	C_6H_5	-	-	60	67	$C_{23}H_{19}N_5O_2S$	64.3 (64.3)	4.4 (4.4)	16.3 (16.3)
11b	H	C_4H_3O	H	*p*-Cl.C_6H_4	61	83	$C_{28}H_{20}N_3O_3S_2Cl$	61.5 (61.5)	3.6 (3.6)	7.6 (7.6)
c	H	C_4H_3O	H	*p*-N$(CH_3)_2$.C_6H_4	58	103	$C_{30}H_{26}N_4O_3S_2$	64.8 (64.9)	4.6 (4.6)	10.0 (10.1)
d	H	C_4H_3O	C_6H_5	C_6H_5	51	121	$C_{34}H_{25}N_3O_2S_2$	69.4 (69.5)	4.2 (4.2)	7.1 (7.1)
e	H	CH=CH.C_6H_5	H	*p*-Cl.C_6H_4	48	87	$C_{32}H_{24}N_3O_2S_2Cl$	66.0 (66.0)	4.1 (4.1)	7.1 (7.1)
f	H	CH=CH.C_6H_5	H	*p*-N$(CH_3)_2C_6H_4$	51	154	$C_{34}H_{30}N_4O_2S_2$	69.0 (69.1)	5.0 (5.0)	9.2 (9.4)
g	H	CH=CH.C_6H_5	H	C_6H_5	57	171	$C_{38}H_{29}N_3O_2S_2$	73.0 (73.1)	4.5 (4.6)	6.7 (6.7)
h	H	*p*-Cl.C_6H_4	H	*o*-Cl.C_6H_4	51	74	$C_{30}H_{21}N_3O_2S_2Cl_2$	61.0 (61.0)	3.5 (3.5)	7.0 (7.1)
i	H	*p*-Cl.C_6H_4	H	*p*-N$(CH_3)_2$.C_6H_4	56	111	$C_{32}H_{27}N_4O_2S_2Cl$	64.1 (64.1)	4.4 (4.5)	9.1 (9.3)

Contd...

Table I—Characterization data of compounds **7-12** (Contd..)

Compd	R_1	R_2	R_3	R_4	Yield (%)	m.p. (°C)	Mol. formula	Found(%) (Calcd) C	H	N
j	H	*p*-Cl.C_6H_4	C_6H_5	C_6H_5	55	116	$C_{36}H_{26}N_3O_2S_2Cl$	68.3 (68.4)	4.1 (4.1)	6.4 (6.6)
k	H	*o*-Cl.C_6H_4	C_6H_5	C_6H_5	53	118	$C_{36}H_{26}N_3O_2S_2Cl$	68.3 (68.4)	4.1 (4.1)	6.4 (6.6)
l	C_6H_5	C_6H_5	H	*p*-$N(CH_3)_2C_6H_4$	50	161	$C_{38}H_{32}N_4O_2S_2$	71.1 (71.2)	5.0 (5.0)	8.7 (8.7)
12b	H	C_4H_3O	H	***p***-Cl.C_6H_4	55	32	$C_{22}H_{16}N_5O_3SCl$	56.6 (56.7)	3.3 (3.4)	15.0 (15.0)
c	H	C_4H_3O	H	*p*-$N(CH_3)_2C_6H_4$	50	53	$C_{24}H_{22}N_6O_3S$	60.7 (60.7)	4.6 (4.6)	17.7 (17.7)
d	H	C_4H_3O	C_6H_5	C_6H_5	49	66	$C_{28}H_{21}N_5O_3S$	66.2 (66.2)	4.0 (4.1)	13.7 (13.8)
e	H	-CH=CH.C_6H_5	H	*p*-Cl.C_6H_4	53	44	$C_{26}H_{20}N_5O_2SCl$	62.1 (62.2)	3.9 (3.9)	13.9 (13.9)
f	H	-CH=CH.C_6H_5	H	*p*-$N(CH_3)_2C_6H_4$	58	70	$C_{28}H_{26}N_6O_2S$	65.8 (65.8)	5.0 (5.0)	16.2 (16.4)
g	H	-CH=CH.C_6H_5	C_6H_5	C_6H_5	55	85	$C_{32}H_{25}N_5O_2S$	70.8 (70.9)	4.5 (4.6)	12.8 (12.8)
h	H	*p*-Cl.C_6H_4	H	-Cl.C_6H_4	48	29	$C_{24}H_{17}N_5O_2SCl_2$	56.4 (56.4)	3.3 (3.3)	13.6 (13.7)
i	H	*p*-Cl.C_6H_4	H	*p*-$N(CH_3)_2C_6H_4$	51	64	$C_{26}H_{23}N_6O_2SCl$	60.1 (60.1)	4.4 (4.4)	16.1 (16.2)
j	H	*p*-Cl.C_6H_4	C_6H_5	C_6H_5	55	68	$C_{30}H_{22}N_5O_2SCl$	65.2 (65.2)	3.9 (3.9)	12.4 (12.6)
k	H	*o*-Cl.C_6H_4	C_6H_5	C_6H_5	56	67	$C_{30}H_{22}N_5O_2SCl$	65.2 (65.2)	3.9 (3.9)	12.4 (12.6)
l	C_6H_5	C_6H_5	H	*p*-$N(CH_3)_2C_6H_4$	63	74	$C_{32}H_{28}N_6O_2S$	68.5 (68.5)	5.0 (5.0)	14.9 (15.0)

albino rats (weighing 80-115 g). The rat paw oedema was produced by the method of Winter *et al.*[6] The percentage inhibition of inflammation was calculated by applying Newbould formula[7]. In this test the most active compounds were **11c, f, g, 1** (58%, 72%, 52% and 75%) and **12a,c,d,f,g,1** (58%, 66%, 50%, 83%, 80% and 75%) inhibition respectively and their activity was compared with phenylbutazone (94% inhibition) at a dose of 4 mg/kg b.w.

Anticonvulsant activity

The compounds **11a-l** and **12a-l** were screened for their anticonvulsant activity against the pentylene tetrazole induced convulsion in albino rats of either sex (weighing 80-115 g) by the method given in literature[8,9]. The compounds were suspended in 5% aq. gum acacia to give a concentration of 25% (w/v). The test compounds were injected i.p. at a dose of 50 mg/kg b.w. 4 hr after the administration of compounds. The rats were injected with pentylenetetrazole (50 mg/kg). Compounds **11f,g,l** and **12f,g** provided 80, 70, 60, 50 and 40% protection respectively against the pentylenetetrazole induced convulsions in rats compared to 100% activity of phenobarbitone (a reference drug) at 50 mg/kg b.w.).

Analgesic activity

The synthesised compounds **11a-l** and **12a-l** were tested for their analgesic activity in albino rats (weighing 80-115 g) by Eddy and Leimbach method[10] at an oral dose 25 mg/kg b.w. Acetyl salicylic acid was employed as a standard drug. The

synthesised compounds **11a,b,c,i** and **12b,c,g** were found to show 158.41, 183.29, 253.16, 281.81, 147.5, 173.49 and 222.19% analgesic activity respectively.

Antimicrobial activity

The compounds **9-12** were screened for their antibacterial activity against *Bacillus subtilis*, *Salmonella typhimurium* and *Escherichia coli* and antifungal activity against *Candida albicans*, *Fusarium heterosporium* and *Aspergillus niger* by filter paper disc technique[11,12] at two concentrations (25 and 50 μg/ml). Standard antibacterial streptomycin and antifungal griseofulvin were also screened under similar conditions for comparison. The compounds **11f,l** and **12c,f,g,l** had good antibacterial activity while compounds **11c,f,l** and **12a,f,l** were found to have pronounced antifungal activity.

Experimental Section

Melting points were taken in an open capillary tube and are uncorrected. IR spectra (KBr) were recorded on an Acculab-10 spectrophotometer ($\upsilon max_{\text{ in cm-1}}$) and PMR spectra in $CDCl_3$ on 90 MHz on Varian CFT-20 instrument using TMS as an internal standard (chemical shifts in δ, ppm).

Ethyl ethanoate phenothiazine 3/benzotriazole 4. Ethyl chloroacetate (0.05mole) was added to a solution of phenothiazine/benzotriazole (0.05 mole) and anhyd. K_2CO_3 (3 g) in ethanol and the reaction mixture was refluxed for 15 hr. Solvent was removed ***in vacuo*** and the residue was crystallised from chloroform to give **3**, yield 82%, m.p. 203° (Found: C,67.3; H,5.2; N,4.8. $C_{16}H_{15}O_2NS$ requires C,67.4; H,5.3; N,4.9%); IR: 3020, 1580, 925, 755, 740, 680 and 650 (phenothiazine nucleus), 1720(>C=O ester); PMR: 1.20(t,3H,J = 7Hz, -$COOCH_2CH_3$), 4.10(q, 2H, J = 7Hz: $COOCH_2CH_3$), 3.60(s, 2H, N-CH_2), 7.20-7.90 (m, 8H, Ar-H); MS: 285(M^+). **4**: Yield 83%, m.p. 40° (Found: C,58.5; H,5.3; N,20.4. $C_{10}H_{11}O_2H_3$ requires C,58.5; H,5.4; N,20.5%); IR: 3020, 1620, 1485, 865, 725 (benzotriazole nucleus), 1715(>C=O); PMR: 1.20 (t, 3H, J = 7Hz, $COOCH_2CH_3$), 3.60(s, 2H, N-CH_2), 4.10(q, 2H, J = 7Hz, $COOCH_2CH_3$), 7.30-7.80(m, 4H, Ar-H); MS: 205(M^+).

Acetohydrazido phenothiazine 5/benzotriazole 6. A mixture of **3/4** (0.028 mol) and hydrazine hydrate (100%; 0.028 mole) was Orefluxed on a steam bath for 5 hr, cooled and filtered to get compounds **5/6**. **5**: Yield 76%, m.p. 170° (Found: C,61.9; H, 4.6; N,15.3. $C_{14}H_{13}ON_3S$ requires C,62.0; H,4.8; N,15.5%); IR:3350-3200(- $NHNH_2$), 1660(>C=O, amido); PMR; 2.50(s, 2H, -NH_2), 3.65 (s, 2H, N-CH_2), 7.10-7.80(m, 8H, Ar-H), 8.20 (s, 1H, CONH); MS: 271(M^+). **6**:Yield 60%, m.p. 85° (Found: C,50.2; H,4.7; N,36.5. $C_8H_9ON_5$ requires C,50.3; H,4.7; N,36.6%); IR: 3350($NHNH_2$), 1660(>C=O, amido); PMR: 2.50(s, 2H, NH_2), 3.65 (s, 2H, N-CH_2), 7.90 (s, 1H, CONH), 7.40-7.70 (m, 4H, Ar-H); MS: 191(M^+).

Arylidene acetohydrazido phenothiazine 7a/benzotriazole 8a. A mixture of **5a/6a** (0.0036 mole), furfuraldehyde (0.0036 mole) and 2-3 drops of gl. acetic acid in ethanol (26 mL) was refluxed on a steam bath for 5 hr. The solvent was removed under reduced pressure to yield a product **7a/8a** respectively, **7a**: Yield 82%, m.p. 143° (Found: C,65.1; H,4.2; N,12.0%. $C_{19}H_{15}N_3O_2S$ requires C,65.3; H,4.2; N,12.0%); IR: 3300-3290(-NH-), 1670(>C=O), 1620(-CH=N-); PMR: 4.40(s, 1H, -N=CH-), 3.70(s, 2H, N-CH_2), 8.00 (s, 1H, -CONH-). and 7.00-7.90 (m, 11H, Ar-H); MS:349(M^+). **8a**: Yield 58%, m.p.76° (Found: C,57.9; H,4.0; N,26.0%. $C_{13}H_{11}N_5O_2$ requires C,57.9; H,4.0; N,26.0%); IR: 3300-3280 (-NH-), 1680(>C=O), 1620(-CH=N-); PMR: 4.50(s, 1H, -N=CH-), 3.70 (s, 2H, N-CH_2), 8.10 (s, 1H, -CONH) and 7.30-7.90(m, 7H, Ar-H); MS: 269(M^+). Other compounds **7b-e** and **8b- e** were prepared from **5** and **6** similarly using different carbonyl compounds. Characterization data are presented in Table I.

2 Aryl-3-[phenothiazino 9a/benzotriazolo 10a acetamidyl]-1,3- thiazolidine-4-ones. To a stirred solution of **7a/8a** (0.0025 mole) in dioxane containing a pinch of anhyd. $ZnCl_2$, mercaptoacetic acid (0.0025 mole) was added and the mixture was refluxed on a steam bath for about 12 hr. Solvent was distilled off at reduced pressure and recrystallized from methanol/chloroform to yield compounds **9a** and **10a** respectively. **9a**: Yield 60%, m.p. 148° (Found: C,59.4; H,4.0; N,9.8%. $C_{21}H_{17}N_3O_3S_2$ requires C,59.5; H,4.0; N,9.9%); IR: 3240 (-NH-), 1715(>C=O, cyclic), 1670(>C=O, amidyl); PMR: 3.20(s, 1H, CHN-), 3.40(s, 2H, CH_2-S-), 3.70 (s, 2H, NCH_2), 8.60 (s, 1H, CONH) and 7.10-7.90 (m, 11H, Ar-H); MS: 423(M^+). **10a**: Yield 65%, m.p.78° (Found: C,52.4; H,3.7; N, 20.3%. $C_{15}H_{13}N_5O_3S$ requires C,52.4; H,3.7; N,20.4%); IR: 3240-3220(-NH-), 1720(>C=O, cyclic), 1670(>C=O, amidyl); PMR: 3.20(s, 1H, -CHN-), 3.40(s, 2H, CH_2S), 3.70

(s, 2H, NCH_2), 8.50(s, 1H, -CONH-) and 7.40-7.90 (m, 7H, Ar-H); MS: 343(M^+). Other compounds **9b-e** and **10b-e** were synthesised in the similar way using **7b-e** and **8b-e** respectively. Characterisation data are presented in Table I.

5-arylidene-2-aryl-3-[phenothiazino 11a/benzotriazolo 12a acetamidyl]-1,3-thiazolidine-4-ones. Equimolar solution of **9a/10a** (0.0015 mole) and cinnamaldehyde in dioxane in the presence of C_2H_5ONa was refluxed for 3 hr on a steam bath and the solvent was removed under reduced pressure. The products so obtained were recrystallised from ethanol to give **11a** and **12a** respectively. **11a**: Yield 52%, m.p.76° (Found: C, 67.0; H, 4.1; N, 7.7%, $C_{30}H_{23}N_3O_3S_2$ requires C, 67.0; H, 4.2; N, 7.8%); IR: 3340(-NH-), 1715(>C=O, cyclic), 1650(>CO; amidyl), 1630(>C=CHAr); PMR: 3.20 (s, 1H, -CHN-), 3.60(s, 2H, -NCH_2), 5.20 (s, 1H, >C=CHAr), 8.70 (s, 1H, -CONH), 7.10-8.00(m, 16H, Ar-H); MS: 537(M^+). **12a**: Yield 57%, m.p. 47°(Found: C,63.0; H, 4.1; N,15.2%. $C_{24}H_{19}N_5O_3S$ requires C,63.0; H, 4.1; N, 15.3%); IR: 3330(-NH-), 1720(>C=O cyclic), 1650(>C=O, amidyl), 1620(>C=CHAr); PMR: 3,30(s, 1H, CHN), 3.60 (s, 2H, $NHCH_2$), 5.20(s, 1H, >C=CHAr), 8.70 (s, 1H, CONH), 7.10-8.00(m, 12H, Ar-H); MS: 457(M^+). Other compounds **11b-l** and **12b-l** were synthesised similarly from **9b-e** and **10b-e** respectively and carbonyl compounds. Characterization data are presented in Table I.

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