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Note

Syntheses of 1,5–benzothiazepines: Part XIX–Syntheses of 10-substituted benzopyranobenzothiazepines as prospective cardiovascular agents

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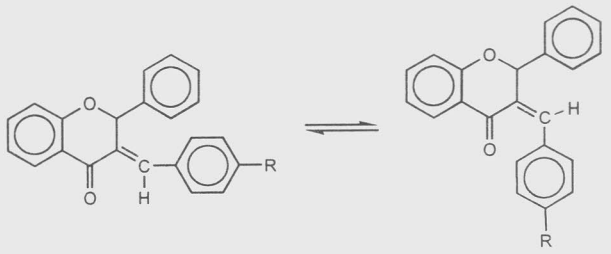
10-Substituted-2-chloro-6a,7-dihydro-6*H*-7-(4-substituted phenyl)-6-phenyl-[1]benzopyrano[3,4-*c*] [1,5] benzothiazepines **3a-l** have been synthesized by reacting (*E*)-6-chloro-3-(4-chloro / methoxybenzylidene) flavanones **2a, b** with 5-substituted-2-aminobenzenethiols **1a-f** by reflux heating in dry toluene containing piperidine (1:1). The products have been tested for purity by TLC and microestimation of nitrogen. IR and ^{1}H NMR and mass spectral studies have enabled the assignment of structures. Bioassay screening of **3e,f,h** and **i** show mild analgesic and anticonvulsant activity.

Compounds having a 1,5-benzothiazepine nucleus have been found to be chemotherapeutically useful showing CVS activities, such as coronary vasodilation[1], calcium antagonists[2], blood platelet aggregation inhibitors[3], antiischemics[4], antihyper-tensives[5], antiarrhythmics[6], etc. Compared to most widely used 1,5-benzothiazepine drug, diltiazem[7], last five years have witnessed the upsurge of relatively more effective cardiovascular drug, clentiazem[8], which possesses a substituent in the fused benzene ring of 1,5-benzothiazepine nucleus. Incorporation of additional heterocyclic ring as a pharmacophore in the 1,5-benzothiazepine nucleus has resulted into the patented compound of useful bioactivity[9]. Proceeding on these lines, we reported the syntheses of compounds having tetracyclic ring system in which benzopyran heterocyclic ring system is fused with benzothiazepine possessing a substituent in the fused benzene ring of the latter[10]. In continuation, we report here the syntheses of 10-subtituted-2-chloro-6a, 7-dihydro-6*H*-7-(4-substituted phenyl)-6-phenyl-[1]benzopyrano-[3,4-*c*][1,5]benzothiazepines.



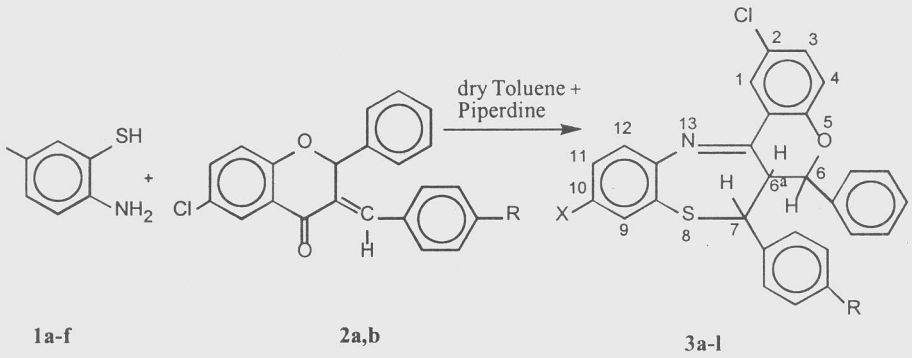
(trans-form) (cis-form)

Figure 1

The syntheses of the title compounds were effected by reacting unsaturated ketones having a,b-unsaturation exocyclic to carbonyl group i.e. (*E*)-6-chloro-3-(4-chloro/methoxy benzylidene) flavanones **2a,b** with six 5-substituted-2-aminobenzenethiols where the substituents are halo-fluoro, chloro, bromo; alkyl-methyl; alkoxyl-methoxyl and ethoxyl **1a-f** by reflux heating for nearly 6-20 hr in dry toluene and piperidine (1:1). The arylidene flavanones **2a,b** were prepared by acid catalyzed condensation of 6-chloroflavanone with 4-chlorobenzaldehyde and 4-anisaldehyde respectively. 6-Chloroflavanone was prepared by reacting 5-chloro-2-hydroxy acetophenone with benzaldehyde in ethanol in the presence of 50% NaOH[11].

Compound **2** having an exocyclic double bond in conjugation with a carbonyl group can exist as structures having cis- and trans-configuration (Figure 1). The trans-form is proved by the allylic coupling constants in the range, 2.1-2.25 Hz in the proton NMR spectra[12]. A broad singlet at δ 6.9 (**2a**),δ 7.22 (**2b**) correspond to the methine proton at C-2 and another broad singlet at δ 7.2 (**2a**),δ 7.42 (**2b**) correspond to the vinyl proton.

The reaction occurs via nucleophilic attack by the sulphydryl electrons of thiol group on the vinyl



1a-f 2a,b 3a-l

Scheme I

carbon of arylidene flavanone which is rendered electrophilic due to vinyl-carbonyl conjugation. This is followed by condensation reaction between the amino group of the thiol and the carbonyl group resulting into the formation of final cyclyzed product (dehydrative cyclization), benzopyrano-benzothiazepines (**3a-l**, Scheme I).

Characterization of the products was done on the basis of analytical (Table-I) and spectral studies.

Infrared spectra of all compounds **3a-l** showed a sharp absorption band at 1602-1612 cm^{-1} which may be assigned to C=N stretching frequency of heterocyclic ring[13]. IR of **3e-l** displayed sharp absorption bands and comparatively weaker ones in the range, 1230-1200 and 1038-1078 cm^{-1} corresponding to aralkyl etheral linkage. Presence of chlorine was also observed as one or two sharp bands at 680-695 and 750-790 cm^{-1} Absence of absorption bands at 1670-1680 (CO) and at 3450-3350 cm^{-1} (NH_2) indicated absence of these groups in the products. The ^1H NMR spectra of all compounds showed a number of peaks in the region, δ 3.6 to 3.9. A doublet at δ 3.85-3.89 (J=12.11-12.21 Hz) may be due to C-7 proton. Another doublet at δ 3.81-3.84 with J=1.6-1.8 Hz was assigned to the C-6 proton. A comparatively weak double doublet absorption at δ 3.67-3.73 was assigned to the bridgehead proton at C-6a. Further, a singlet at δ 3.84 (3H) corresponding to methoxyl protons appeared in the spectra of **3g-l**. On the basis of coupling constants, $J_{H\text{-}7,\ H\text{-}6a}$=12.11-12.21 Hz and $J_{H\text{-}6,H\text{-}6a}$=1.6-1.8 Hz, it is assumed that the hydrogen atoms at the two adjacent carbon atoms, C-7 and C-6a adopt trans arrangement[12(a)].

Bioassay screening

It was carried out for four compounds **3e, f, h, i** as given below :

Effect on respiration, cardiovascular system and nictitating memb-rane contraction. Adult cats of either sex, anaesthesised with pentobarbitone sodium (30 mg/kg i.v.) were employed. The trachea was cannulated and connected to Marey's tambour, one of the common carotid arteries, was cannulated and connected to a mercury monometer. Records were made on a slow moving kymograph. The compounds were administered through a cannulated femoral vein.

Each compound was administered in doses of 1 and 5 mg/kg i.v. Effect on respiration was assessed on rate and amplitude. The effect on blood pressure was studied from the common carotid artery through an indwelling cannula on a kymograph. The effect of the compounds was observed on the blood pressure per se and also on the blood pressure responses of adrenaline (2-4 μg), acetylcholine (1-2 μg), histamine (1-2 μg) and isoprenaline (1-2 μg). The contraction of one of the nictitating membranes, due to electrical stimulation of sympathetic nerve, was also recorded through a system of pulleys and frontal writing level on the kymograph.

Gross effects and effects on central nervous system. These were studied in mice of either sex between 15 and 20 g. Initial testing was done at 100 mg/kg dose using 5 animals. Gross effects were observed for 2 hrs after drug administration for any evidence of CNS stimulation or depression or any autonomic effect. This involved noting the effect on (i) spontaneous motor activity, (ii) certain

Table I– Physical constants and microanalytical data of 10-substituted-2-chloro-6a,7-dihydro-6*H*-7-(4-substituted phenyl)-6-phenyl-[1]benzo-pyrano[3,4-*c*][1,5]benzothiazepines **3a-l**

Compd.3	R	X	Mol Formula $[M]^+$,$[M+2]^+$	m.p. (°C)	Yield (%)	N analysis (%)Found (Calcd.)
a	Cl	F	$C_{28}H_{18}NSOFCl_2$,(505,507)	110-115	45	2.80 (2.79)
b	Cl	Cl	$C_{28}H_{18}NSOCl_3$	132-136	45	2.72 (2.70)
c	Cl	Br	$C_{28}H_{18}NSOCl_2Br$	110	50	2.51 (2.49)
d	Cl	CH_3	$C_{29}H_{21}NSOCl_2$	108	67	2.83 (2.81)
e	Cl	OCH_3	$C_{29}H_{21}NSO_2Cl_2$	82	61	2.75 (2.73)
f	Cl	OC_2H_5	$C_{30}H_{23}NSO_2Cl_2$,(531,533)	85	62	2.66 (2.65)
g	OCH_3	F	$C_{29}H_{21}NSO_2FCl$, (501,503)	88	58	2.79 (2.77)
h	OCH_3	Cl	$C_{29}H_{21}NSO_2Cl_2$	120	65	2.70 (2.68)
I	OCH_3	Br	$C_{29}H_{21}NSO_2ClBr$	88	50	2.50 (2.47)
j	OCH_3	OCH_3	$C_{30}H_{24}NSO_2Cl$, (497,499)	118	62	2.78 (2.80)
k	OCH_3	OCH_3	$C_{30}H_{24}NSO_3Cl$	72	59	2.72 (2.70)
l	OCH_3	OC_2H_5	$C_{31}H_{26}NSO_3Cl$, (527,529)	88	63	2.67 (2.65)

reflexes e.g. writhing, corneal or pinnal, (iii) muscletone (reduced and catalepsy), (iv) posture and gait (ataxia and writhing), (v) eyes (pupil and ptosis), (vi) respiration and (vii) observing them for occurrence of tremors, convulsions, Straub's tail, piloerection, cyanosis and body temperature.

Analgesic screening was carried out by Haffner's Tail Clip Method[14]. Failure to produce the painful vocalization and self biting of the tails indicates the analgesic activity. The Supramaximal Electroshock Seizure Pattern Test was carried out by delivering a current stimulus of 48 mA through an electroconvulsiometer using ear electrodes. In saline treated controls, it produces tonic extension of the hind limbs. Block of convulsions indicates anticonvulsant activity.

However, none of the four compounds (**3e**, **3f**, **3h** and **3i**; Table-I) exhibited any marked activity for further follow-up studies.

Experimental Section

Melting points are uncorrected. IR spectra were recorded in KBr pellets on a Perkin Elmer Infracord 881 spectrophotometer, PMR spectra in $CDCl_3$ on a Jeol FT NMR 400 MHz spectrometer using TMS as internal standard and mass spectra on a varian Match-7 instrument at 70 ev. Purity of the compounds was checked by TLC on silica gel 'G' coated glass plates using toluene : ethyl acetate (7:3) as irrigant.

5-chloro-2-hydroxyacetophenone[15] and 5-substituted-2-aminobenzenethiols16 were prepared by literature methods.

6-chloro-3-(4-substituted-benzylidene) flavanone 2. Equimolar quantities of 6-chloroflavanone (0.01 mole, 2.575 g) and 4-chlorobenzaldehyde/4-methoxybenzaldehyde (0.01 mole, 1.405/1.36 g) were dissolved in dry ethanol (50 mL). To this reaction mixture, hydrogen chloride gas was passed with gentle heating and stirring till the colour of the reaction mixture changed from yellow to dark red. The reaction mixture was kept at room temperature for 24 hr and crystallization of the crude solid from dry methanol afforded the arylidene flavanone, 6-chloro-3-(4-chloro benzylidene) flavanone **2**a, yellow crystals, m.p. 128-30°C, yield 2.48 g (65%) and 6-chloro-3-(4-methoxy-benzylidene) flavanone **2**b, pinkish brown amorphous solid, m.p. 85°C, yield 2.11 g (56%).

10-Ethoxy-2-chloro-6a, 7-dihydro-6*H*-7-(4-methoxyphenyl)-6-phenyl-[1]benzopyrano [3, 4-*c*] [1,5] benzothiazepines 3l. 2-Amino-5-ethoxybenzenethiol (0.001 mole, 0.169 g) and 6-chloro-3-(4-methoxybenzylidene) flavanone (0.001 mole, 0.376 g) were taken in dry toleune (5 mL) containing dry piperidine (5 mL). The reaction mixture was refluxed for 22 hrs till one of the reactants disappeared which was noticed by tlc monitoring. Solvent was removed to obtain an

amorphous solid which was crystallized from dry methanol, yield 0.30 g (58%), m.p. 88°C, [TLC R_f 0.92]; (Found: N, 2.67%. $C_{31}H_{26}NSO_3Cl$ requires N 2.65%); MS : m/z $[M]^+$ 527, $[M+2]^+$ 529; PMR :δ 1.49 (t, 3H, J = 6 Hz), 4.12 (q, 2H, J = 6Hz), C-10-OC_2H_5], 3.73 (dd, 1H, H-6a), 3.83 (d, 1H, J=1.8Hz, H-6), 3.87 (d, 1H, J = 12.12 Hz, H-7), 3.84 (3H, s, OCH_3), 6.85-8.08 (m, 15 H, ArH).

Similarly **3a-k** were prepared. However, **3a-f** required refluxing for 6-10 hrs whereas **3g-k**, for 20-22 hr.

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