SYNTHESIS AND PHARMACOLOGICAL ACTIVITY OF CERTAIN 6-ALKYL/ ARALKYL-7-NITRO[1]BENZOPYRANO[2,3-B][1,5]BENZODIAZEPIN-13-ONES

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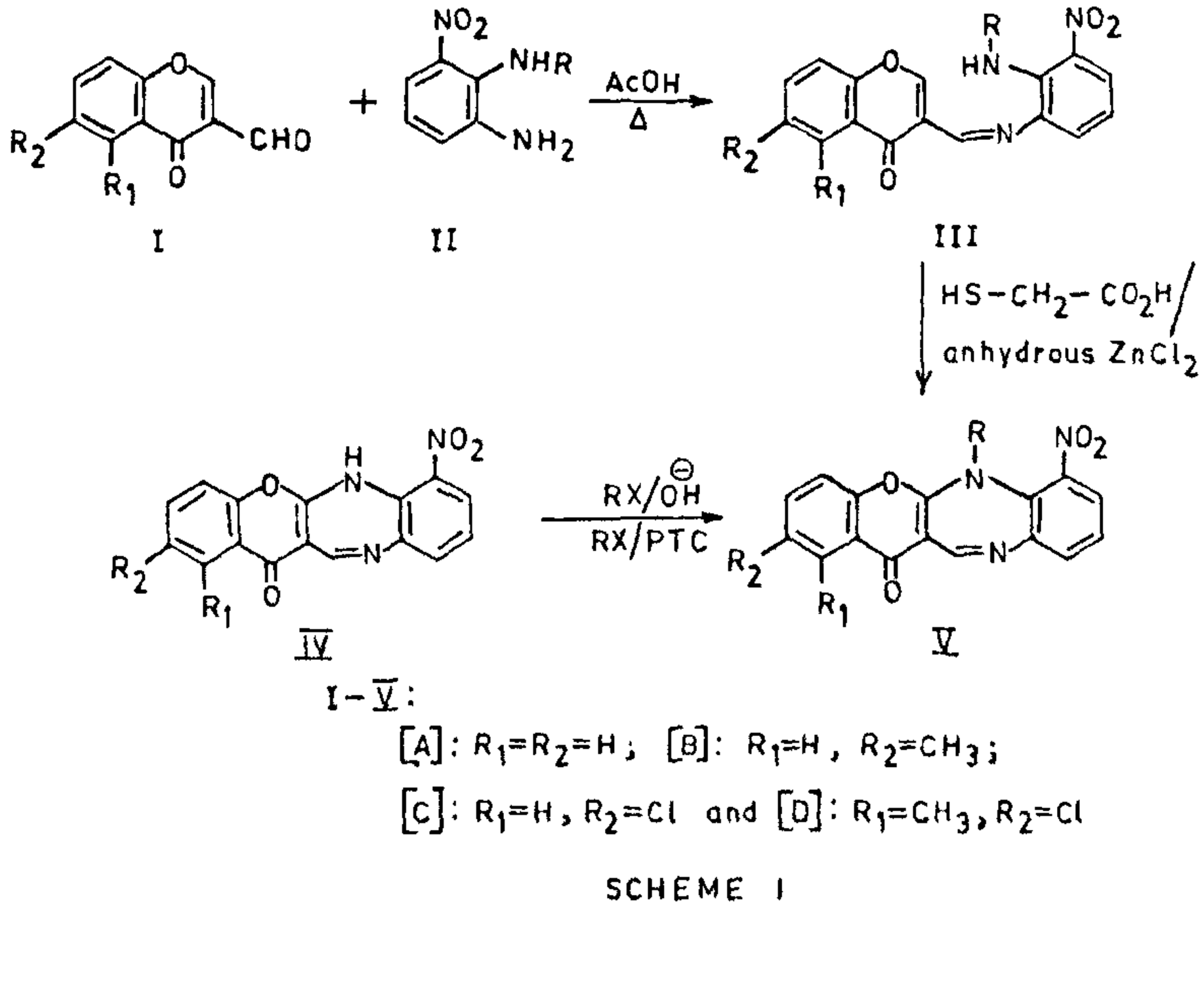
ABSTRACT

Twelve 3-(N-[2-(alkylamino/aralkylamino)-3-nitrophenyl]formimidoyl)-chromones on heating with thioglycolic acid over anhydrous zinc chloride yielded the respective 6-alkyl/aralkyl-7-nitro[1]benzopyrano[2,3-b][1,5]benzodiazepin-13-ones. The products obtained on N-substitution of 7-nitro[1]benzopyrano[2,3-b][1,5]benzodiazepin-13(6H)-ones have been characterized on comparison with the authentic samples. They have been screened for pharmacological activity using experimental animals.

INTRODUCTION

In continuation of our work on the synthesis and pharmacological evaluation of the new benzodiazepinones and their derivatives[1-5], it has been considered necessary to synthesize the title compounds through different routes and screen them for pharmacological activity.

For this purpose twelve 3-{N[2-(alkylamino/aralkylamino)-3-nitrophenyl]formimidoyl} chromones (III) were prepared[3]. Each of III on heating with thioglycolic acid over anhydrous zinc chloride afforded a yellow crystalline solid which has been characterized as the corresponding 6-alkyl/aralkyl-7-nitro-[1]benzopyrano[2,3-b][1,5]benzodiazepin-13-ones (V) on the basis of analytical and spectral data. For example, (V), R = CH_2Ph, R_2 = CH_3: IR spectrum of the compound showed absence of the secondary amino (NH–CH_2–Ph) group, a cyclized product resulting from the participation of the group in a Michael addition; PMR spectrum (in $CDCl_3$; δ ppm) showed signals at 2.62 (*s*, 3H, Ar–CH_3), 5.2 (*s*, 2H, N–CH_2–Ph), 7.15–8.24 (*m*, 9H, Ar–H), 8.35 (*dd*, 1H, *J* = 2 Hz and 9 Hz,



SCHEME I

C_5–H), 9.12 (*d*, 1H, C_1–H) and 9.51 (*s*, 1H, C_{12}–H). Similarly, eleven more title compounds were prepared and characterized. Physical and analytical data for these compounds are presented in table 1.

For synthesis of (V) by another route, four different 7-nitro[1]benzopyrano[2,3-b][1,5]benzodiazepin-13(6H)-ones (IV) were prepared as reported earlier and subjected to N-substitution (methylation, ethylation, benzylation and benzoylation) by the conventional as well as the phase-transfer catalysis[2] methods. The products of N-substitution (except in the case of benzoylation) have been identified as the respective 6-alkyl/aralkyl-7-nitro[1] benzopyrano[2,3-b][1,5]-benzodiazepin-13-ones (V), on comparison with the products obtained by unambiguous synthesis (scheme 1). The products of benzoylation have, however, been characterized by analogy and satisfactory spectral data. The IR spectra of benzoylated products showed the absence of secondary amino (–NH) and, on the other hand, showed another absorption at 1730 cm^{-1} characteristic of (N–CO–Ph) in addition to the chromone carbonyl group at 1640 cm^{-1}.

EXPERIMENTAL

Melting points were determined in open capillaries using Toshniwal melting point apparatus and are uncorrected. IR spectra were recorded on a Perkin-Elmer Infracord-283 spectrophotometer, in nujol, and PMR spectra on a Varian EM-360 spectrometer using TMS as an internal standard. Mass spectra were recorded on Jeol JMS-D 300 at 70 eV.

3-Formylchromones and N^2-alkyl/aralkyl-3-nitro-*o*-phenylenediamines[1,3] and 7-Nitro[1]-benzopyrano[2,3-b][1,5]benzodiazepin-13(6H)-ones[1] were prepared as reported earlier.

Table 1 *Physical and analytical data for 6-substituted 7-nitro-[1]benzopyrano [2,3-b] [1,5]benzodiazepin-13-ones*

Compd. No.	Substituent *R*	Molecular formula	m.p. (°C)	Solvent for recrystallization	% Nitrogen, obs. (calc.)
[A] $R_1=R_2=H$					
1	CH_3	$C_{17}H_{11}N_3O_4$	>320	Alcohol	13.08(13.02)
2	C_2H_5	$C_{18}H_{13}N_3O_4$	220	Alcohol	12.52(12.60)
3	CH_2Ph	$C_{23}H_{15}N_3O_4$	110	Benzene	10.52(10.43)
4	COPh	$C_{23}H_{13}N_3O_5$	200	Benzene : chloroform (1 : 1)	10.20(10.14)
[B] $R_1=H$; $R_2=CH_3$					
5	CH_3	$C_{18}H_{13}N_3O_4$	310	Benzene	12.52(12.45)
6	C_2H_5	$C_{19}H_{15}N_3O_4$	300	Chloroform	12.02(12.11)
7	CH_2Ph	$C_{24}H_{17}N_3O_4$	102	Benzene : chloroform (1 : 1)	10.29(10.23)
8	COPh	$C_{24}H_{15}N_3O_5$	135	DMF	9.83(9.74)
[C] $R_1=H$; $R_2=Cl$					
9	CH_3	$C_{17}H_{10}N_3O_4Cl$	180	Benzene : chloroform (1 : 1)	11.79(11.89)
10	C_2H_5	$C_{18}H_{12}N_3O_4Cl$	150	Chloroform	11.36(11.29)
11	CH_2Ph	$C_{23}H_{14}N_3O_4Cl$	120	Benzene : chloroform (1 : 1)	9.73(9.86)
12	COPh	$C_{23}H_{12}N_3O_5Cl$	140	-do-	9.37(9.32)
[D] $R_1=CH_3$; $R_2=Cl$					
13	CH_3	$C_{18}H_{12}N_3O_4Cl$	200	Alcohol	11.34(11.39)
14	C_2H_5	$C_{19}H_{14}N_3O_4Cl$	230	DMF	10.94(10.88)
15	CH_2Ph	$C_{24}H_{16}N_3O_4Cl$	106	Benzene : chloroform (1 : 2)	9.42(9.36)
16	COPh	$C_{24}H_{14}N_3O_5Cl$	130	Chloroform	9.40(9.47)

All compounds are yellow in colour; Satisfactory analyses for C and H were also recorded; Yields were in the range of 62–85%.

6-Alkyl/aralkyl-7-nitro[1]benzopyrano[2,3-b][1,5] benzodiazepin-13-ones (V)—General procedure

To a mixture of 3-{N-[2-(alkylamino/aralkylamino)-3-nitrophenyl]formimidoyl}chromone ((III) 0.001 mol) and thioglycolic acid (0.012 mol) taken in a round-bottomed flask, dry benzene (50 ml) and anhydrous zinc chloride (0.1 g) were added. The reaction mixture was heated under reflux for 2 h on a water-bath. Benzene was removed by distillation and the residual liquid was poured on to a little crushed ice, while stirring. The resulting product was filtered at pump, washed repeatedly with ice-cold water, and dried. The product was purified by recrystallization from suitable solvent.

The N-substitution of 7-nitro[1]benzopyrano[2,3-b][1,5]-benzodiazepin-13(6H)-ones (IV) was carried out following the procedure described earlier[2].

PHARMACOLOGICAL ACTIVITY

Acute toxicity

Healthy, random-bred mice weighing 25–30 g were fasted overnight and administered CMC–Na suspensions of the test compounds in graded doses. Each dose group consisted of five mice. The mice were kept under observation for four days after administering the test compounds and the LD_{50} values were determined[6] (table 2).

The animals were closely observed during the toxicity studies for symptoms such as convulsions, hypersensitivity, piloerection and ptosis, and sleep.

Potentiation of pentobarbitone-induced narcosis

Healthy and adult mice weighing 20–30 g were fasted for 24 h and divided into groups of six each. The test compounds were administered intraperitoneally as their gum acacia suspensions at a dose of 100 mg/kg body weight. After 30 min the animals were given a solution of pentobarbitone-sodium intraperitoneally at a dose of 60 mg/kg body weight. Control animals were administered the same dose of pentobarbitone-sodium. After one hour, observations were made of test and control animals and the numbers of animals which had lost the righting reflex were determined. The percentage hypnosis for each of the test compounds was calculated[7]. The data are presented in table 2.

Analgesic and anti-inflammatory activity

Analgesic activity was assayed by two different methods, viz., the tail-clip method[8] and the writhing method[9], at a dose of 100 mg/kg body weight in

Table 2 *Pharmacological data for 6-substituted 7-nitro[1]benzopyrano-[2,3-b] [1,5] benzodiazepin-13-ones (V)*

Compound	LD_{50} value (i.p.)	Pentobarbitone-induced hypnosis* (% effect)	Analgesic activity* (% protection)		Anti-inflammatory activity* (% inhibition of rat-paw oedema)
			Tail-clip	Writhing	
1	>1000	−10	20	20	35
2	>1000	−10	20	25	25
3	>1000	−20	35	40	48
4	>1000	−25	30	35	35
5	>1000	−35	35	38	50
6	>1000	−30	40	40	35
7	>1000	−40	50	52	65
8	>1000	−50	40	35	50
9	800	−50	45	50	50
10	800	−50	48	50	58
11	750	−60	60	65	65
12	850	−60	50	55	50
13	900	−35	25	20	25
14	950	−35	25	30	25
15	800	−45	40	40	55
16	850	−50	30	35	40

*Determined at a dose of 100 mg/kg body weight.
− Indicates CNS depressant activity.

albino mice (table 2). It was calculated by using the formula:

$$\text{Percentage protection} = 100 - \frac{\text{No. of test animals responding}}{\text{No. of control animals responding}} \times 100.$$

The anti-inflammatory activity was determined at a dose of 100 mg/kg body weight by the rat-paw oedema method[10] in albino rats of either sex weighing 80–100 g. Carrageenin (1% solution) was employed as the phlogistic agent. The rat-paw volume difference was measured by Maqlab's differentiometer and the percentage inhibition of oedema was calculated using the formula:

Percentage inhibition of oedema $= 100 - [1 - (Vt/Vc)]$ where, Vt is the volume of the paw of the treated animal, and VC, the volume of the paw of the control animal. Aspirin and phenylbutazone were employed as the standards. The results are presented in table 2.

RESULTS AND DISCUSSION

It is evident from the LD_{50} values (table 2) that the compounds of series A and B are safer than those of the other series. The toxicity of compounds of series C is higher when compared to that of compounds of series D may be due to the presence of the chloro substituent alone. It is a unique feature that the compounds with benzyl group at 1-position are relatively more toxic. It may be noticed that the benzopyrano-benzodiazepinones with a 7-nitro group (this report) are relatively more toxic than their counterparts with a 9-nitro group [4]. The present compounds had a potentiating effect on pentobarbitone-induced hypnosis. The compounds of series C, which have a chloro substituent, are observed to be more effective in this regard. Among the compounds of this series, those with benzyl or benzoyl group are more potent. A similar observation was made with regard to analgesic and anti-inflammatory activity. Again, benzyl group was found to have a potentiating effect.

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