Short Communication

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New Reserpine Analogues

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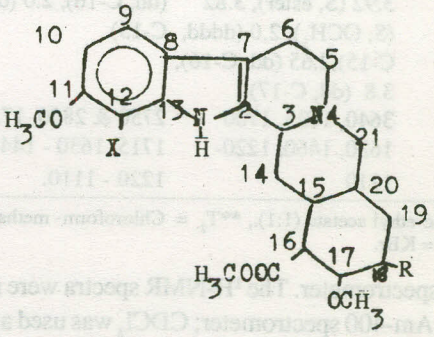
Three new reserpine analogues were synthesised by Vilsmeier reaction and the product were identified as 12-formyl resrpine (III), 12-carboxy reserpine (IV) and 12-formyl rescinnamine (V) by spectroscopic means. Reserpine like activity of III, IV and V were evaluated.

Reserpine (I) was widely used in the treatment of hypertension and a variety of mental ailments [1-3]. Due to its pronounced biological activity a large number of reserpine derivatives had been synthesised [4-7]. However, analogues having reserpine skeleton possessed considerable reserpine like acitivity. This idea was proved successful when reserpine was nitrated and nitro reserpine was found to have same order of pharmaceutical action with none of its side effects [8-11]. In veiw of these findings, it seemed intresting to extend these studies for the preparation of few more reserpine analogues using Vilsmeier reaction [12-14] and to study their pharmacological properties.

Reserpine (I) and rescinnamine (II) after reaction with Vilsmeier reagent in chloroform gave 12-formyl derivatives. The products were separated by thick layer chromatography and struture were confimred by means of spectroscopy.

Physical constants and other spectroscopic data of compounds I, II, III, IV and V are given in Tables 1-2. Biological testing of III, IV and V revealed hypotensive and sedative activity slightly less than reserpine. However compound V exhibited some analgesic property as well.

MPS were determined in glass capillaries and are uncorrected. Mass spectra were obtained on a Finnigan MAT



I. X = H
III. X = CHO
IV. X = COOH
Where;
R = 3,4,5-trimethoxy benzoyl

II. X = H
V. X = CHO =
where;
R = 3,4,5-trimethoxy cinnamoyl

Table 1. Physical Constant and Spectroscopic Data of Compound I, III, IV.

	Compound - I	Compound - III	Compound - IV
M. p. (°C)	[15] 262 - 3°	184 - 186°	300 - 302° (dec.)
R_f	95*	82*	75
	85**	60**	52
Mass spectra	608 (M^+), 593, 577, 397, 381 365 & 195	637 (M + 1), 609,395, 212 & 195	652 (M^+), 483, 424,271 & 211
^{1}H-NMR (δ)[a]	[18] 7.40 (S, C-12), 7.34 (J = 7.6 Hz, d, C-9), 7.31 (S, benzoyl proton) 6.8 (J=8.6 Hz, d, C-10) 7.6 (S,NH) 3.90 (S, ester) 3.85 (S, OCH_3), 2.05 (dddd, C-15), 2.69 (dd, C-16) 3.8 (dd, C-17).	7.34 (J = 7.6 Hz, d, C-9, 7.30 (S, benzoyl proton), 6.7 (J=8.7 Hz, d, C-10), 3.85 (S, ester) 7.6 (S,N-H), 3.80 (S, OCH_3), 2.05 (dddd, C-15), 2.69(dd,C-15), 3.8 (dd, C-17).	9.0 (S, COOH), 7.30 (S, benzoyl proton) 6.8 (J=7.8 Hz, d, C-10) 7.24 (J=7.3 Hz, d, C-9), 7.5 (S, NH) 3.95 (S, ester),3.85 (S, -OCH_3) 3.8 (dd, C-17), 2.69 (dd, C-16), 2.05 (dddd, C-15).
IR[b] (cm^{-1})	[16] 3500, 1710 (b) 1460, 1220, 1110	2750 & 2850, 1735, 1715, 1620-1440, 1220&1110	3600-2400, 1735, 1710, 1620-1440 1220, 1110
UV[c] (nm)	[17] 216, 267, 296	190, 210, 385	165, 185 & 400

* T_1 = Benzene - ethyl acetate (1:1); ** T_2 = Chloroform - methanol (4:1); a = $CDCl_3$; b = KBr; c = CH_3 OH.

TABLE 2. PHYSICAL CONSTANTS AND SPECTROSCOPIC DATA OF COMPOUND II AND V.

	Compund– II	Compund – V
Mp (°C)	237-238° (d)	254° (d)
R_f	90*	80*
	80*	65*
Mass spectra	634(M), 606, 591, 575, 394 & 195	662 (M), 634, 606 395, 212 & 195
^{1}H-NMR (δ)*	[18] 7.34 (J = 17Hz, d, cinnamic proton), 7.62 (J=17 Hz,d, cinnamic proton),7.3 (J=7.8Hz, d, C-9) 6.78 (J=8.9Hz,d, C-10),7.6 (S, N-H) 3.92 (S, ester), 3.82 (S, OCH_3), 2.0 (dddd, C-15),2.65 (dd, C-16), 3.8 (dd, C-17).	7.60 (J= 17 Hz, d cinnamic proton), 7.34 (J=15Hz, cinnamic proton), 7.4 (J=7.8Hz, d, C-9), 6.85 (J=9 Hz, d, C-10), 3.90 (S, ester),3.85 (S,OCH_3) , 3.8 (dd, C-17), 2.65 (dd, C-16), 2.0 (dddd, C-15).
IR[b](cm)	3640, 1725, 1700 1630, 1460, 1220-1110	2750 & 2850, 1730 1715, 1630 - 1440 1220 - 1110.

*T_1 = Benzene-ethyl acetate (1:1)., **T_2 = Chloroform- methanol (4:1)., a = $CDCl_3$, b = KBr.

112 S mass spectrometer. The ^{1}H-NMR spectra were recorded on a Bruker Am-400 spectrometer; $CDCl_3$ was used as solvent and TMS as internal standard. IR and UV spectra were taken on JASCO IRA-I and Pye Unicam SP-80Z spectrometers.

12-Formyl reserpine. 0.5g, 0.822mM of reserpine in 20 ml chloroform was added to 1.0 ml of formylating mixture* (previously kept for 45 mins at O°). The reaction mixture was kept for overnight at room temperature and was worked up by the addition of water (contained small amount of CH_3COONa). 12- formyl reserpine was separated by thick layer chromatography. It melted at 302° (d) and analysed for $C_{33}H_{39}N_2O_9$.CHO; C=64.35%; H = 6.17%; N=4.35%, calculated for $C_{33}H_{39}N_2O_9CHO$; C = 64.15%; H = 6.29%; N = 4.40% yield, 0.15 g, 30%.

12-Carboxy reserpine. 0.8 ml of formylating mixture* was introduced into the reserpine solution (0.25 g, 0.411 mM reserpine in 20 ml of chloroform) and the reaction mixture was kept for 72 hrs at room temperature. It was worked up by the addition of water and extracted by ethyl acetate. The 12-carboxy reserpine was separated by thick layer chromatography. Found; C = 62.7%; H = 6.03%; N = 4.1%, calculated for $C_{33}H_{39}N_2O_9$. COOH, C=62.25%, H=6.34%, N=4.25% yield, 0.1g = 40%.

12-Formyl rescinnamine. In 10 ml of rescinnamine solution (containing 0.1 g, 0.315 mM rescinnamine), 0.8 ml of formylating mixture was introduced. The reaction mixture was kept for 36 hrs at room temperature and was worked up according to the procedure used for 12-formyl reserpine (III). 12-Formyl rescinnamine melted at 254° (d) and analysed for $C_{35}H_{41}N_2O_9$. CHO found ;C = 65.25%; H = 6.34%; N = 4.23%, yield, .03g = 30%.

* Formylating mixture was prepared by mixing N, N-dimethyl formamide and thionyl chloride (3:2, v/v).

Key words : Synthesis, Vilsmeier reaction, Reserpine.

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