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Synthesis and Antihypertensive Activity of Certain Mannich Bases of 2-Ethoxycarbonylindoles and 5*H*-Pyridazino[4,5-b]indoles

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This manuscript reports the synthesis of two series of Mannich Bases 3-12 and 21-40 obtained respectively by the reaction of either 2-ethoxycarbonylindoles 1-2 or 5H-pyridazino [4,5-b]inoles 17-20 as a substrate with formalin and the appropriate 2° amines under the suitable Mannich conditions. Fourteen of the synthesized Mannich basese were screened as antihypetensive agents in normotensive anesthetized rats. The effect of compound 4 in normotensive anesthetized dogs was also studied.

Key words: 2-Ethoxycarbonylindoles, 5*H*-Pyridazino[4,5-b]indoles, Mannich bases, Antihypertensive activity

INTRODUCTION

The indole nucleus forms the basis of a series of compounds of both therapeutic and chemical interest. The most therapeutically useful indole derivatives that exhibited potential antihypertensive activity are those incorporated a tryptamine residue (Glamokowski *et al.*, 1977; Helsley *et al.*, 1978; Archibald *et al.*, 1980). The Indoramin (Archibald *et al.*, 1971) is an example of these compounds. Moreover, the intensive researches given by Monge and co-workers (Monge *et al.*, 1978, 1987, 1988) on 5H-pyridazino[4,5-b]indoles, the structure analog of the antihypertensive agent Hydralazine (Recee, 1981), showed antihypertensive activity. In addition, although various Mannich bases at C-3 of indole derivatives are well known, information regarding the use of 2-ethoxycarbonylindoles as substrate in Mannich reactions is recognized only in two papers (Takami *et al.*, 1985; Wadia *et al.*, 1987) and is not reported for 3,4-dihydro-4-oxo-5H-pyridazino[4,5-b]indoles, so far. Therefore, the prepared molecules may be matter of request both biologically and chemically.

MATERIALS AND METHODS

Chemistry

Melting points were measured in open capillary tubes using a Gallenkamp melting point apparatus and are uncorrected. Elemental analyses were carried out at the Microanalytical Unit, Cairo university. Infrared spectra were recorded using Shimadzu IR 435 Spectrophotometer. Proton magnetic resonance were obtained using Jeol FX 90 Q (90 MHz) Spectrometer. TLC were performed on silica gel using $CHCl_3$-Petroleum ether 40/60 (7:3) and spots were visualized by their fluorescence at 254 nm in UV.

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General Procedure for preparation of Mannich bases of 2-ethoxycarbonylindoles (3-12)

To an ice cold solution of the appropriate secondary amine (2 mmol) is added 37% formalin (0.44 ml, 6 mmol) and acetic acid (0.73 ml). The appropriate 2-ethoxycarbonylindole **1,2** (2 mmol) in ethanol (10 ml) is then added and the resulting mixture was heated on boiling water-bath for 1-2 h (TLC). Most of the solvent was removed under reduced pressure and the resulting semisolid product was purified on column chromatography containing silica gel and using chloroform as eluent (Table I). The hydrochloride form of the prepared Mannich bases was obtained by passing dry HCl gas in ethereal solution of the base (Table I).

General procedure for preparation of 2-ethoxycarbonyl-3-formylindoles (13,14)

Freshly distilled phosphoryl chloride (3.8 ml) was added slowly with stirring and cooling to freshly distilled dimethylformamide (10 ml) and the temperature was maintained

Table I. Physical and Spectral Data of Compounds **3-12**

Compd. No.	R	R^1	M.P. °C (HCl salt)	Yield %	Mol. Form. (mol. wt.)[a]	IR (KBr) ν, cm^{-1} C=O N-H	^{1}H-NMR ($CDCl_3$, δ=ppm)
3[b]	H	A	82-83 (203-205)	92	$C_{14}H_{18}N_2O_2$ (246)	1685 3300	1.46 (t, 3H, *J*=7 Hz, CH_3), 2.32 (s, 6H, $N(CH_3)_2$), 3.97 (s, 2H, NCH_2), 4.46 (q, 2H, *J*=7 Hz, OCH_2), 7.21-7.82 (m, 4H, Ar-H), 9.01 (s.br., 1H, NH)
4	H	B	103-104 (178-180)	88	$C_{16}H_{22}N_2O_2$ (274)	1680 3330	1.07 (t, 6H, $2CH_3$), 1.43 (t, 3H, *J*=7 Hz, CH_3), 2.68 (q, 4H, $2CH_2$), 4.14 (s, 2H, NCH_2), 4.54 (q, *J*=7H, 2H, OCH_2), 7.19-7.87 (m, 4H, Ar-H), 8.90 (s.br., 1H, NH)
5	H	C	85-86 (144-146)	82	$C_{16}H_{20}N_2O_2$ (272)	1685 3200	1.43 (t, 3H, *J*=7 Hz, CH_3), 1.78-1.95 (m, 4H, $(CH_2)_2$), 2.36 (t, 4H, $N(CH_2)_2$), 4.22 (s, 2H, NCH_2), 4.48 (q, 2H, *J*=7H, OCH_2), 7.21-7.86 (m, 4H, Ar-H), 8.87 (s.br., 1H, NH)
6	H	D	108-109 (125-127)	87	$C_{17}H_{22}N_2O_2$ (286)	1680 3310	(t, 3H, *J*=7H, CH_3), 1.37-1.47 (br., 6H, $(CH_2)_3$), 2.59-2.65 (br., 4H, $N(CH_2)_2$), 4.01 (s, 2H, NCH_2), 4.46 (q, 2H, *J*=7H, OCH_2), 7.25-7.82 (m, 4H, Ar-H), 8.90 (s.br., 1H, NH)
7	H	E	133-134 (203-205)	90	$C_{16}H_{20}N_2O_3$ (288)	1680 3310	1.34 (t, 3H, *J*=7 Hz, CH_3), 2.80 (t, 4H, *J*=4.4 Hz, $2CH_2$), 3.71 (t, 4H, *J*=4.4 Hz, $O(CH_2)_2$), 4.01 (s, 2H, NCH_2), 4.46 (q, 2H, *J*=7 Hz, OCH_2), 7.23-7.82 (m, 4H, Ar-H), 8.9 (s.br., 1H, NH)
8	Br	A	132-134 (222-224)	94	$C_{14}H_{17}BrN_2O_2$ (324.9)	1680 3300	(t, 3H, *J*=7 Hz, CH_3), 2.30 (s, 6H, $N(CH_3)_2$), 3.90 (s, 2H, NCH_2), 4.45 (q, 2H, *J*=7 Hz, OCH_2), 7.16 (d, 1H, C_7-H), 7.42 (d, 1H, C_6-H), 8.12 (s, 1H, C_4-H), 9.09 (s.br., 1H, NH)
9	Br	B	118-120 (223-225)	92	$C_{16}H_{21}BrN_2O_2$ (352.9)	1680 3310	1.07 (t, 6H, *J*=7 Hz, $2CH_3$), 1.42 (t, 3H, *J*=7 Hz, CH_3), 2.62 (q, 4H, *J*=7H, $N(CH_2)_2$), 4.14 (s, 2H, NCH_2), 4.42 (q, 2H, *J*=7 Hz, OCH_2), 7.15 (d, 1H, C_7-H), 7.44 (d, 1H, C_6-H), 8.10 (s, 1H, C_4-H), 9.09 (s.br., 1H, NH)
10	Br	C	152-154 (220-222)	86	$C_{16}H_{19}BrN_2O_2$ (350.9)	1680 3300	1.43 (t, 3H, CH_3), 1.76-1.98 (m, 4H, $(CH_2)_2$), 2.60 (t, 4H, N $(CH_2)_2$), 4.14 (s, 2H, NCH_2), 4.46 (q, 2H, OCH_2), 7.16 (d, 1H, C_7-H), 7.42 (d, 1H, C_6-H), 8.05 (s, 1H, C_4-H), 9.09 (s.br., 1H, NH)
11	Br	D	155-157 (186-187)	82	$C_{17}H_{21}BrN_2O_2$ (364.9)	1685 3305	1.42 (t, 3H, *J*=7 Hz, CH_3), 1.36-1.47 (br., 6H, $(CH_2)_3$), 2.58-2.62 (br., 4H, $N(CH_2)_2$), 4.90 (s, 2H, NCH_2), 4.45 (q, 2H, *J*=7 Hz, OCH_2), 7.25 (d, 1H, C_7-H), 7.37 (d, 1H, C_6-H), 8.12 (s, 1H,A r-H at C_4), 8.90 (s.br., 1H, NH)
12	Br	E	132-134 (226-228)	88	$C_{16}H_{19}BrN_2O_3$ (366.9)	1680 3300	1.43 (t, 3H, *J*=7 Hz, CH_3), 2.54 (t, 4H, *J*=4.4 Hz, $N(CH_2)_2$), 3.69 (t, 4H, *J*=4.4 Hz, $O(CH_2)_2$), 4.01 (s, 2H, NCH_2), 4.46 (q, 2H, *J*=7 Hz, OCH_2), 7.25 (d, 1H, C_7-H), 7.37 (d, 1H, C_6-H), 8.12 (s, 1H, C_4-H), 8.92 (s.br., 1H, NH)

[a]Satisfactory elemental analyses for C, H, N; A=$N(CH_3)_2$; B=$N(CH_2CH_3)_2$; C=pyrrolidinyl; D=piperidyl; E=morpholinyl. [b]Reported in two papers (Takami *et al.*, 1985; Wadia *et al.*, 1987).

between 0-5°C. After complete addition, the mixture was stirred at room temperature for 30 min. To this solution, the appropriate 2-indolecarboxylate **1,2** (25 mmol) in dimethylfomamide (7.5 ml) was added in portion with constant cooling and stirring. The reaction mixture was stirred for 2 h and the temperature of the reaction was kept below 60°C. The resulting yellowish-green solution was diluted with 10% sodium hydroxide solution (pH 8) and the mixture heated on a steam-bath just to boiling. The solid product which separated on cooling was filtered, washed with water and recrystallized from ethanol.

2-Ethoxycarbonyl-3-formylindole (13)

m.p. 191-192°C (Monge *et al.*, 1987), IR (KBr, ν cm^{-1}): 1650 (C=O aldehyde), 1700 (C=O ester), 3300 (NH). PMR ($CDCl_3$, δ ppm): 1.58 (t, 3H, CH_3), 4.72 (q, 2H, CH_2), 7.51-7.74 (m, 4H, Ar-H), 8.94 (s, 1H, NH), 11.04 (s, 1H, CHO).

5-Bromo-2-ethoxycarbonyl-3-formylinole (14)

m.p. 243-245°C (Cavallini and Ravenna, 1958), IR (KBr, ν cm^{-1}): 1635 (C=O aldehyde), 1720 (C=O ester), 3140 (NH). PMR ($CDCl_3$, δ ppm): 1.58 (t, 3H, CH_3), 4.76 (q, 2H, CH_2), 7.62 (d, 1H, C_7-H), 7.78 (d, 1H, C_6-H), 8.42 (s, 1H, C_4-H), 8.92 (s, 1H, NH), 11.03 (s, 1H, CHO)

General procedure for preparation of 2-ethoxycarbonyl-1-ethyl-3-formylindoles (15, 16)

To a mixture of benzene (20 ml) containing ethyl iodide (4.68 g, 0.03 mol), 50% aqueous sodium hydroxide solution (10 ml) and benzyltriethylammonium chloride (0.22 g, 1 mmol), the appropriate 2-ethoxycarbonyl-3-formylindole **13,14** (0.02 mol) was added. The mixture was stirred at room temperature until indole could not longer detected by monitoring the reaction using TLC. The mixture was then diluted with water (20 ml). The organic layer was separated, washed with dilute hydrochloric acid (5 ml) and then with water (10 ml). The organic layer was dried over anhydrous magnesium sulfate. The solvent and the excess ethyl iodide was removed under reduced pressure and the residue was recrystallized.

2-Ethoxycarbonyl-1-ethyl-3-formylindole (15)

m.p. 95-96°C (pet.ether 40/60), yield 4 g (82%), *Anal. Calcd.* for $C_{14}H_{15}NO_3$ (245): C, 68.75, H, 6.12, N, 5.71. Found: C, 69.00, H, 6.30, N, 5.40. IR (KBr, ν cm^{-1}): 1650 (C=O aldehyde), 1700 (C=O ester). PMR ($CDCl_3$, δ ppm): 1.57 (t, 3H, CH_3), 1.61 (t, 3H, CH_3), 4.75 (q, 2H, NCH_2), 4.81 (q, 2H, OCH_2), 7.53-8.95 (m, 4H, Ar-H), 11.07 (s, 1H, CHO).

5-Brom-2-ethoxycarbonyl-1-ethyl-3-formylindole (16)

m.p.135-136°C (ethanol), yield 4.5 g (70%), *Anal. Calcd.* for $C_{14}H_{14}BrNO_3$ (323.9): C, 51.86, H, 4.32, N, 4.32. Found: C, 51.70, H, 4.20, N, 4.60. IR (KBr, n cm^{-1}): 1650 (C=O aldehyde), 1710 (C=O ester). PMR ($CDCl_3$, d ppm): 1.59 (t, 3H, CH_3), 1.62 (t, 3H, CH_3), 4.78 (q, 2H, CH_2), 4,83 (q, 2H, CH_2), 7.60 (d, 1H, C_7-H), 7.82 (d, 1H, C_6-H), 8.91 (s, 1H, C_4-H), 11.0 (s, 1H, CHO).

General procedure for preparation of 3,4-dihydro-4-oxo-5H-pyridazino [4,5-b]inoles (17-20)

To a solution of the appropriate 2-ethoxycarbonyl-3-formylindole **13-16** (46.25 mmol), 90% hydrazine hydrate (7.0 g, 140 mmol) is added. The yellowish-green coloured mixture is heated under reflux for 6 h. On cooling, yellowish-white precipitate is separated, filtered, washed with water and recrystallized.

3,4-Dihydro-4-oxo-5H-pyridazino[4,5-b]indole (17)

m.p. 324-326°C (ethanol) (Monge *et al.*, 1978), IR (KBr, ν cm^{-1}): 1635 (C=O), 3150-2850 (NH/OH).PMR (DMSO-d_6, δ, ppm): 7.62-7.95 (m, 4H, Ar-H), 9.10 (s, 1H, C_1-H), 13.42 (s, 2H, 2 NH).

8-Bromo-3,4-Dihydro-4-oxo-5H-pyridazino[4,5-b]indole (18)

m.p. above 350°C (DMF/ethanol), yield: 9.2 g (75%), *Anal. Calcd.* for $C_{10}H_6BrN_3O$ (263.9): C, 45.47, H, 2.27, N, 15.91. Found: C, 45.20, H, 2.40, N, 16.10 IR (KBr, ν cm^{-1}): 1640 (C=O), 3300-2800 (NH/OH). PMR (DMSO-d_6, δ ppm): 7.98 (d, 1H, C_6-H), 8.18 (d, 1H, C_7-H), 8.88 (s, 1H, C_9-H), 9.21 (s, 1H, C_1-H), 13.54 (s, 2H, 2 NH).

3,4-Dihydro-5-ethyl-4-oxo-5H-pyridazino[4,5-b]indole (19)

m.p.: 226-227°C (ethanol), yield: 7 g (71%), *Anal. Calcd.* for $C_{12}H_{11}N_3O$ (213): C, 67.60, H, 5.16, N, 19.71. Found: C, 67.40, H, 5.0, N, 19.90. IR (KBr, ν cm^{-1}): 1655 (C=O), 3250 (NH). PMR (DMSO-d_6, δ ppm): 1.52 (t, 3H, CH_3), 5.02 (q, 2H, CH_2), 7.61-8.12 (m, 4H, Ar-H), 9.14 (s, 1H, C_1-H), 13.39 (s, 1H, NH).

8-Bromo-3,4-dihydro-5-ethyl-4-oxo-5H-pyridazino[4,5-b] indole (20)

m.p.: 278-280°C (ethanol), yield: 8.1 g (60%), *Anal. Calcd.* for $C_{12}H_{10}BrN_3O$ (291.9): C, 49.33, H, 3.42, N, 14.38. Found: C, 49.10, H, 3.80, N, 14.50. IR (KBr, ν cm^{-1}): 1650 (C=O), 3160-2800 (NH). PMR (DMSO-d_6, δ ppm): 1.62 (t, 3H, CH_3), 5.07 (q, 2H, CH_2), 8.19 (d, 1H, C_6-H), 8.29 (d, 1H, C_7-H), 8.82 (s, 1H, C_9-H), 9.21 (s, 1H, C_1-H), 13.42 (s, 1H, NH).

General procedure for preparation of Mannich bases of 5*H*-pyridazino [4,5-b]indoles (21-40)

To an ice cold solution of the appropriate 2° amine (2 mmol) ia added 37% formalin (0.44 ml, 6 mmol). The appropriate pyridazino[4,5-b]indole **17-20** (2 mmol) in ethanol (10 ml) is then added and the resulting mixture was heated on boiling water-bath for 1 h. Most of the solvent was removed under reduced pressure and the resulting solid was recrystallized (Table II, III).

Antihypertensive activity in normotensive anesthetized rats

The compounds were studied on adult normotensive anesthetized (ip injection of 400 mg/Kg urethane and 30

Table II. Physical and IR Spectral Data of Compounds **21-40**

Compd. No.	R	R^1	R^2	M.P. °C	Yield %	Mol.Form. (mol.wt.)a	IR (KBr) ν, cm^{-1} C=O	N-H
21	H	A	H	216-217	78	$C_{13}H_{14}N_4O$ (242)	1640	3200
22	H	B	H	207-208	72	$C_{15}H_{18}N_4O$ (270)	1640	3220
23	H	C	H	168-169	72	$C_{15}H_{16}N_4O$ (268)	1640	3100
24	H	D	H	241-243	68	$C_{16}H_{18}N_4O$ (282)	1640	3100
25	H	E	H	248-250	82	$C_{15}H_{16}N_4O_2$ (284)	1640	3220
26	H	A	H	107-108	72	$C_{15}H_{18}N_4O$ (270)	1645	
27	H	B	H	72-73	68	$C_{17}H_{22}N_4O$ (298)	1645	
28	H	C	H	148-149	67	$C_{17}H_{20}N_4O$ (296)	1650	
29	H	D	H	144-145	73	$C_{18}H_{22}N_4O$ (310)	1640	
30	H	E	H	155-156	76	$C_{17}H_{20}N_4O_2$ (312)	1640	
31	Br	A	Et	263-265	75	$C_{13}H_{13}BrN_4O$ (310.9)	1630	3200
32	Br	B	Et	222-224	76	$C_{15}H_{17}BrN_4O$ (348.9)	1640	3200
33	Br	C	Et	227-229	70	$C_{15}H_{15}BrN_4O$ (346.9)	1640	3200
34	Br	D	Et	285-287	67	$C_{16}H_{17}BrN_4O$ (360.9)	1645	3200
35	Br	E	Et	290-292	68	$C_{15}H_{15}BrN_4O_2$ (362.9)	1630	3200
36	Br	A	Et	131-132	62	$C_{15}H_{17}BrN_4O$ (348.9)	1655	
37	Br	B	Et	99-100	60	$C_{17}H_{21}BrN_4O$ (376.9)	1655	
38	Br	C	Et	160-161	55	$C_{17}H_{19}BrN_4O$ (374.9)	1655	
39	Br	D	Et	179-181	62	$C_{18}H_{21}BrN_4O$ (388.9)	1655	
40	Br	E	Et	150-151	66	$C_{17}H_{19}BrN_4O_2$ (390.9)	1640	

[a]Satisfactory elemental analyses for C, H, N; A=$N(CH_3)_2$, B=$N(CH_2CH_3)_2$, C=pyrrolidinyl, D=piperidyl, E=morpholinyl

Table III. ^{1}H-NMR Spectral Data of Compounds **25-44**

Compd. No.	^{1}H-NMR (DMSO-d_6, δ=ppm)
21	2.36 (s, 6H, $N(CH_3)_2$), 5.05 (s, 2H, NCH_2), 7.31-8.22 (m, 4H, Ar-H), 8.76 (s, 1H, C_1-H), 12.78 (s.br., 1H, NH)
22	1.07 (t, 6H, *J*=7 Hz, $2CH_3$), 2.68 (q, 4H, *J*=7 Hz, $2CH_2$), 5.18 (s, 2H, NCH_2), 7.17-8.25 (m, 4H, Ar-H), 8.75 (s, 1H, C_1-H), 12.88 (s.br., 1H, NH)
23	1.61-1.88 (m, 4H, $(CH_2)_2$), 2.75 (t, 4H, $N(CH_2)_2$), 5.19 (s, 2H, NCH_2), 7.32-8.21 (m, 4H, Ar-H), 8.74 (s, 1H, C_1-H), 12.87 (s.br., 1H, NH)
24	1.35-1.64 (br., 6H, $(CH_2)_3$), 2.56-2.68 (br., 4H, $N(CH_2)_2$), 5.07 (s, 2H, NCH_2), 7.32-8.20 (m, 4H, Ar-H), 8.74 (s,1H, C_1-H), 12.37 (s.br., 1H, NH)
25	2.63 (t, 4H, $N(CH_2)_2$), 3.51 (t, 4H, $O(CH_2)_2$), 5.09 (s, 2H, NCH_2), 7.32-8.23 (m, 4H, Ar-H), 8.77 (s, 1H, C_1-H), 12.76 (s.br., 1H, NH)
26	1.51 (t, 3H, *J*=7 Hz, CH_3), 2.49 (s, 6H, $N(CH_3)_2$), 4.94 (q, 2H, *J*=7 Hz,CH_2), 5.08 (s, 2H, NCH_2), 7.26-7.97 (m,4H, Ar-H), 8.48 (s, 1H, C_1-H)
27	1.15 (t, 6H, *J*=7 Hz, $2CH_3$), 1.48 (t, 3H, *J*=7 Hz, CH_3), 2.80 (q, 4H, $2CH_2$), 4.94 (q, 2H, *J*=7 Hz, CH_2), 5.26 (s, 2H, NCH_2), 7.26-7.96 (m, 4H, Ar-H), 8.46 (s, 1H, C_1-H)
28	1.49 (t, 3H, *J*=7 Hz,CH_3), 1.60-1.82 (m, 4H, $(CH_2)_2$), 2.75 (t, 4H, $N(CH_2)_2$), 4.93 (q, 2H, *J*=7 Hz, CH_2), 5.08 (s, 2H, NCH_2), 7.32-8.19 (m, 4H, Ar-H), 8.43 (s, 1H, C_1-H)
29	1.49 (t, 3H, *J*=7 Hz, CH_3), 1.57-1.77 (m, 6H, $(CH_2)_3$), 2.43-2.72 (br., 4H, $N(CH_2)_2$), 4.94 (q, 2H, *J*=7 Hz, CH_2), 5.18 (s, 2H, NCH_2), 7.26-8.07 (m, 4H, Ar-H), 8.47 (s, 1H, C_1-H)
30	1.48 (t, 3H, *J*=7 Hz, CH_3), 2.81 (t, 4H, *J*=4.4 Hz, $N(CH_2)_2$), 3.71 (t, 4H, *J*=4.4 Hz, $O(CH_2)_2$), 4.90 (q,2H, *J*=7 Hz, CH_2), 5.12 (s, 2H, NCH_2), 7.26-8.15 (m, 4H, Ar-H), 8.41 (s, 1H, C_1-H)
31	2.24 (s, 6H, $N(CH_3)_2$), 5.05 (s, 2H, NCH_2), 7.60 (d, 1H, C_6-H), 7.68 (d, 1H, C_7-H), 8.15 (s, 1H, C_9-H), 8.45 (s, 1H, C_1-H), 12.90 (s.br., 1H, NH)
32	1.15 (t, 6H, *J*=7 Hz, $2CH_3$), 2.79 (q, 4H, *J*=7 Hz, $2CH_2$), 5.24 (s, 2H, NCH_2), 7.66 (d, 1H, C_6-H), 7.72 (d, 1H, C_7-H), 8.14 (s, 1H, C_9-H), 8.40 (s, 1H, C_1-H), 12.87 (s.br., 1H, NH)
33	1.62-1.83 (m, 4H, $(CH_2)_2$), 2.65 (t, 4H, $N(CH_2)_2$), 5.18 (s, 2H, NCH_2), 7.62 (d, 1H, C_6-H), 7.68 (d, 1H, C_7-H), 8.48 (s, 1H, C_9-H), 8.77 (s, 1H, C_1-H), 12.92 (s.br., 1H, NH)
34	1.57-1.87 (br., 6H, $(CH_2)_3$), 2.65-2.78 (br., 4H, $N(CH_2)_2$), 5.05 (s, 2H, NCH_2), 7.60 (d, 1H, C_6-H), 7.78 (d, 1H, C_7-H), 8.45 (s, 1H, C_9-H), 8.77 (s, 1H, C_1-H), 12.87 (s.br., 1H, NH)

Table III. Continued

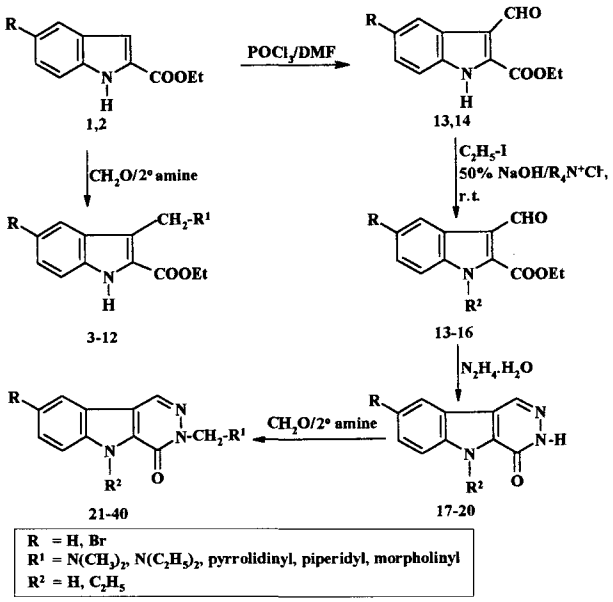
Compd. No.	^{1}H-NMR (DMSO-d_6, δ=ppm)
35	2.61 (t, 4H, *J*=4.4 Hz, $N(CH_2)_2$), 3.53 (t, 4H, *J*=4 Hz, $O(CH_2)_2$), 5.01 (s, 2H, NCH_2), 7.61 (d, 1H, C_6-H), 7.72 (d,1H, C_7-H), 8.46 (s, 1H, C_9-H), 8.78 (s, 1H, C_1-H), 12.88 (s.br., 1H, NH)
36	1.49 (t, 3H, *J*=7 Hz, CH_3), 2.49 (s, 6H, $N(CH_3)_2$), 4.91 (q, 2H, *J*=7 Hz, CH_2), 5.08 (s, 2H, NCH_2), 7.60 (d, 1H, C_6-H), 7.68 (d, 1H, C_7-H), 8.14 (s, 1H, C_9-H), 8.42 (s, 1H, C_1-H)
37	1.14 (t, 6H, $2CH_3$), 1.47 (t, 3H, *J*=7 Hz, CH_3), 2.80 (q, 4H, $2CH_2$), 4.91 (q, 2H, *J*=7 Hz, CH_2), 5.25 (s, 2H, NCH_2), 7.67 (d, 1H, C_6-H), 7.74 (d, 1H, C_7-H), 8.14 (s, 1H, C_9-H), 8.41 (s, 1H, C_1-H)
38	1.56 (t, 3H, *J*=7 Hz,CH_3), 1.67-1.82 (m, 4H, $(CH_2)_2$), 2.86 (t, 4H, $N(CH2)_2$), 4.92 (q, 2H, *J*=7 Hz, CH_2), 5.25 (s, 2H, NCH_2), 7.61 (d, 1H, C_6-H), 7.70 (d, 1H, C_7-H), 8.15 (s, 1H, C_9-H), 8.42 (s, 1H, C_1-H)
39	1.48 (t, 3H, *J*=7 Hz, CH_3), 1.55-1.72 (br., 6H, $(CH_2)_3$), 2.65-2.72 (br., 4H, $N(CH_2)_2$), 4.91 (q, 2H, *J*=7 Hz, CH_2), 5.17 (s, 2H, NCH_2), 7.61 (d, 1H, C_6-H), 7.68 (d, 1H, C_7-H), 8.12 (s, 1H, C_9-H), 8.46 (s, 1H, C_1-H)
40	1.47 (t, 3H, *J*=7 Hz, CH_3), 2.81 (t, 4H, *J*=4.4 Hz,$N(CH_2)_2$), 3.71 (t, 4H, *J*=4.4 Hz, $O(CH_2)_2$), 4.9 (q, 2H, *J*=7 Hz, CH_2), 5.16 (s, 2H, NCH_2), 7.61 (d, 1H, C_6-H), 7.70 (d, 1H, C_7-H), 8.18 (s, 1H, C_9-H), 8.48 (s, 1H, C_1-H)

mg/Kg α-chloralose) rats weighing 180-220 g. Systolic blood pressure was recorded indirectly from the tail artery of groups of 5 animals using the tail-cuff method (Schwartz, 1971). Animals were pre-warmed for 20 min in a ventilated chamber maintained at 39°C prior to each measurement. Experimental materials were administered ip in normal saline when the solubility permitted or suspended in normal saline containing 1.0% (carboxymethyl) cellulose and 2.0% Tween 80 at a dose of 40 mg/kg. Blood pressure was measured after administration at 10, 30, 60, 120, 180 and 240 min. The mean change in systolic blood pressure of each group was calculated and statistical differences in blood pressure of treated and control (vehicle-treated) determined using the Student's t-test (Tallarida and Jacob, 1979).

RESULTS AND DISCUSSION

Chemistry

For the synthesis of Mannich bases **3-12**, 2-ethoxycarbonylindoles **1,2** were reacted with fomalin and the appropriate secondary amines by heating under reflux in ethanol containing drops of acetic acid (Table I). Mannich bases **21-40** were synthesized via a series of chemical reactions as outlined in Scheme 1. Formylation of **1,2** with $POCl_3$/DMF in a similar way to that described for indole (James and Synder, 1959) gave 2-ethoxycarbonyl-3-formylindoles **13,14**. Alkylation of the latter using ethyl iodide was carried out by the phase-transfer catalysis (Barco *et al.*, 1976), using benzyltriethylammonium chloride as catalyst in 50% NaOH/benzene, and yielded 2-ethoxycarbonyl-1-ethyl-3-formylindoles **15,16**. Heating of **13-16** with hydrazine hydrate under reflux gave 5*H*-pyridazino[4,5-b]indoles **17-20**. Refluxing of **17-20** with formalin and the appropriate secondary amine in ethanol gave the *N*-Mannich bases **21-40** (Table II, III). It is worthy to mention that the attempt to prepare the *N*-Mannich bases **21-40** in the hydrochloride forms led to their decomposition and the pyridazinoindoles **17-20**



Scheme 1. Synthesis of Mannich Bases

were liberated. In contrast, the C-Mannich bases **3-12** were stable in acid medium and were obtained in hydrochloride forms (Table I). Structure of all the prepared compounds was confirmed by micro-analytical and spectral data.

Antihypertensive activity

Fourteen of the synthesized Mannich bases were initially screened in the normotensive anesthetized rats. The compounds were administered ip at a dose of 40 mg/kg. The blood pressure was measured at the following times after injection 10, 30, 60, 120, 180 and 240 min. The mean change in systolic blood pressure of each group of 5 animals was calculated. Statistically significant falls in blood pressure were observed with compounds **3, 4, 7, 9** and **12** (Table IV).

Table IV. The Antihypertensive Effect in Normotensive Anesthetized Rat After ip Injection of 40 mg/kg

Compound	Control	Systolic Arterial Blood Pressure (mmHg)					
Number	Mean ± SEM	10 min	30 min	60 min	120 min	180 min	240 min
Vehicle	117 ± 1	115 ± 3	117 ± 2	115 ± 2	116 ± 1	114 ± 2	117 ± 2
3 HCl	119 ± 8	80 ± 11*	72 ± 11*	75 ± 12*	75 ± 12*	84 ± 10*	85 ± 11*
4 HCl	138 ± 4	63 ± 8*	69 ± 9*	61 ± 8*	69 ± 8*	66 ± 9*	73 ± 10*
7 HCl	137 ± 4	90 ± 11*	99 ± 10*	86 ± 11*	84 ± 10*	92 ± 12*	88 ± 9*
9 HCl	116 ± 8	87 ± 9*	80 ± 8*	83 ± 9*	83 ± 10*	91 ± 10*	92 ± 8*
12 HCl	138 ± 3	77 ± 12*	72 ± 11*	74 ± 10*	72 ± 10*	64 ± 9*	63 ± 10*
22	117 ± 4	111 ± 5	109 ± 3	112 ± 2	113 ± 4	111 ± 2	115 ± 3
23	111 ± 4	108 ± 3	110 ± 2	112 ± 3	112 ± 3	109 ± 2	111 ± 3
25	117 ± 1	115 ± 3	112 ± 2	113 ± 4	116 ± 2	116 ± 1	115 ± 2
27	132 ± 4	127 ± 3	128 ± 4	127 ± 2	129 ± 4	132 ± 3	131 ± 2
30	127 ± 5	123 ± 4	122 ± 3	120 ± 5	122 ± 4	123 ± 4	122 ± 3
32	118 ± 8	117 ± 6	112 ± 6	116 ± 7	115 ± 6	117 ± 6	116 ± 7
35	137 ± 4	130 ± 5	129 ± 3	130 ± 4	129 ± 5	132 ± 4	132 ± 3
37	118 ± 5	114 ± 4	115 ± 5	116 ± 3	113 ± 4	114 ± 3	116 ± 4
40	134 ± 6	127 ± 5	123 ± 5	123 ± 3	124 ± 5	126 ± 6	128 ± 7

*Indicates statistically significant changes with respect to the vehicle treated control group
$P<0.05$

The antihypertensive activity of compound **4** was confirmed in barbiturate normotensive anaesthetized three dogs (iv injection of 35 mg/Kg pentobarbital sodium) weighing 12-16 Kg. Following iv injection of 40 mg/Kg of compound **4**, there was marked fall in systolic blood pressure from 120 ± 10 mmHg to 70 ± 10 mmHg. The LD_{50} was found to be 180 mg/kg (in rats, ip).

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