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Note

Synthesis and pharmacological activity of some 2, 3-diphenylindole derivatives

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2, 3-Diphenyl-5-methoxyindole-6-carboxaldehyde **2b** is reacted with semicarbazide hydrochloride to give the corresponding semicarbazide derivative **3** which is cyclized to the triazole **4**. The chalcones **5a** and **5b** have been prepared from the 5-hydroxy- and 5-methoxyindole derivatives **2a** and **2b** respectively by treatment with *p*-aminoacetophenone and these are then cyclized with hydrazine hydrate to **6a** and **6b** respectively. 5-Chloro-2, 3-diphenylindole **7** is converted into the 6-amino derivative **8** by nitration followed by reduction and the amino derivative is then condensed with salicylaldehyde to give the benzoxazepinyl derivative **9**. Compound **8** on treatment with acetonitrile, ethyl isothiocyanate and *o*-chlorophenol yields **10**, **11** and **12** respectively. Compounds **1a, b; 3; 4; 5a, b** and **6a, b** have been tested for their antiinflammatory and analgesic activities. Compounds **1a** and **3** are found to be the more potent antiinflammatory compounds as compared to indomethacin and **3** and **5b** have been found to be more potent than aspirin.

Sulindac and indomethacin, both indole acetic acid derivatives are used as antiinflammatory agent in therapy[1]. A considerable amount of work has been done on the structural variation of the class of drugs broadly known as non-steroidal antiinflammatory drugs (NSAIDS)[2-9]. It has been observed that the best known non-steroidal antiinflammatory drugs (NSAIDS) are acidic in nature. In view of this our attention has been directed on the variation of the aromatic indole moiety by introducing different acidic function groups and cyclization to form 5, 6- and 7-membered heterocyclic ring with a view to synthesize new analogues with improved analgesic[10,11] and antiinflammatory effect.

Formylation of 2, 3-diphenyl-5-hydroxy- or methoxyindole **1a, b** gave the 6-carboxaldehyde derivatives **2a, b**[12] (Scheme I). 2, 3-Diphenyl-5-methoxy-6-carboxaldehyde **2b** was reacted with semicarbazide in acetic acid to form the corresponding semicarbazone derivative **3** which on cyclization with ferric chloride hexahydrate gave the corresponding 1, 3, 4-triazole derivative **4**. On the other hand, compounds **2a, b** were treated with *p*-aminoacetophenone in 10% sodium hydroxide to yield the chalcones **5a, b** which were cyclized with hydrazine hydrate to produce the pyrazoline derivatives **6a, b**.

Nitration of 5-chloro-2, 3-diphenylindole by conc. nitric and sulphuric acid mixture (1:1) followed by reduction using conc. hydrochloric acid and granulated tin afforded the 6-aminoindole derivative **8** which on condensation with salicylaldehyde in dry benzene furnished benzoxazepinyl derivative **9**.

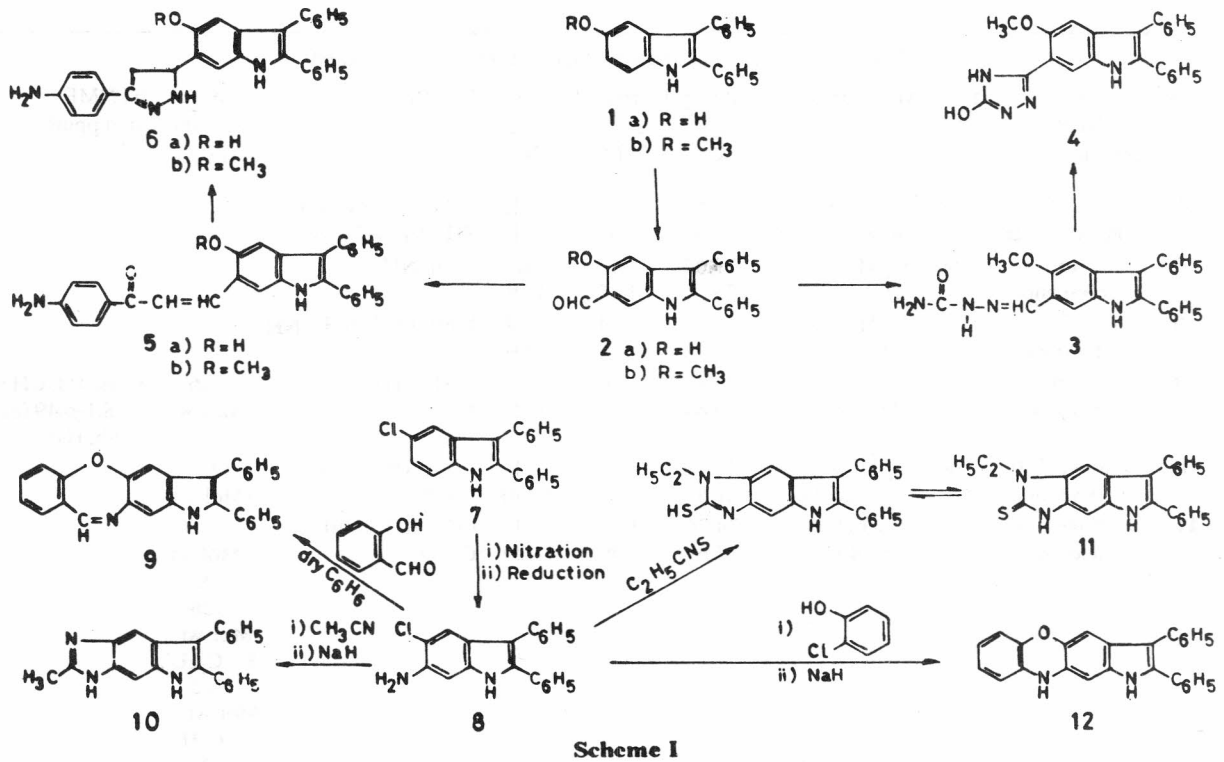
Imidazole derivatives **10** and **11** were prepared by the reaction of **8** with acetonitrile and ethyl isothiocyanate in the presence of sodium hydride. Cyclization of **8** with *o*-chlorophenol in the presence of sodium hydride gave the benzomorpholinyl derivative **12**.

Pharmacological studies

The pharmacological tests were conducted on male albino rats weighing (120-150 g) and the animals were obtained from the Animal House Colony, N.R.C., Cairo, Egypt. They were housed 6 per cage and fed on standard laboratory diet. Water was given *ad libitum*.

Anti-inflammatory effect

Six rats in each group: Group 1 control received 0.5 mL of 20% propylene glycol in water intraperitoneally and then injected subcutaneous with 0.1 of 5% sterile formalin solution in saline into the right hind paw and acts as positive control. Group 2 received indomethacin 20 mg/kg b. wt. as positive control. Group 3-10 received the tested compounds which are **1a, b; 3; 4; 5a, b; 6a, b** in 10 mg/kg, b. wt. in 20% propylene glycol. The acute anti-inflammatory effect were measured according to Winter *et al.*[13], the mean percent oedema was calculated and compared with that of control positive. Results were statistically analysed



Scheme I

Table I—Physical and spectral data of compounds prepared

Compd	m.p. (°C) solvent for crystallization	Yield (%)	Mol. formula	Analysis calcd/(Found) C	H	N	IR (KBr) (cm^{-1})	Mass spectra (m/z)	^1H NMR (δ in ppm)
1a	145 acetone	60	$C_{20}H_{15}N$ (269.259)	89.21 (89.11	5.58 5.49	5.20 5.09)	3400 (OH), 3310 (NH)		8.15 (s, 1H, NH exchangeable D_2O), 7.45-6.75 (m, 13H, Ph, Hs)
1b	120 ethanol	70	$C_{21}H_{17}NO$ (299.334)	84.25 (84.11	5.71 5.51	4.67 4.54)	3300 (NH)		
2a	178-179 Ethanol		$C_{21}H_{15}O_2N$ (313.314)	80.49 (80.35	4.82 4.71	4.47 4.39)	3450-3300 (OH, NH), 1680 (CHO)		
2b	190 ethanol		$C_{22}H_{17}O_3N$ (343.336)	76.95 (76.89	4.98 4.90	4.07 4.00)	3320 (NH), 1690 (CHO)		10.5 (s, 1H, CHO), 8.55 (s, 1H, NH), 7.95-7.05 (m, 12H, Ph, Hs), 4.0 (s, 3H, OCH_3)
3	70 dec. methanol	50	$C_{23}H_{20}N_4O_2$ (384.437)	71.86 (71.76	5.24 5.19	14.57 14.41) 3534	3400-3300 (NH_2, NH), 1671 (−CO− NH), 1620 (C=N)		
4	130 methanol	50	$C_{23}H_{18}N_4O_2$ (382.423)	72.24 (72.13	4.74 4.69	14.65 14.58)	(OH), 3426 (NH), 1630 (C=N)	382 (Mol. wt)	
5a	190 ethanol	60	$C_{29}H_{22}N_2O_2$ (430.482)	80.91 (80.87	5.15 5.05	6.51 6.43)	3570 (OH), 3400-3300 (NH_2, NH), 1710 (C=O)		
5b	210 dec. ethanol	65	$C_{30}H_{24}N_2O_2$ (444.508)	81.06 (81.00	5.44 5.37	6.30 6.26)	3480-3306 (broad NH_2, NH, 1720 (C=O)	444.5 (Mol. wt)	
6a	195 methanol	60	$C_{29}H_{24}N_4O$ (444.514)	78.35 (78.29	5.44 5.40	12.61 12.49)	3580-3310 (broad, OH, NH_2, NH), 1610 (C=N)	444.5 (Mol. wt)	

—Contd.

Table I—Physical and spectral data of compounds prepared

Compd	m.p. (°C) solvent for crystallization	Yield (%)	Mol. formula	Analysis calcd/(Found) C	H	N	IR (KBr) (cm^{-1})	Mass spectra (m/z)	^1H NMR (δ in ppm)
6b	125 Pet. E90-110	55	$C_{30}H_{26}N_4O$ (458.54)	78.58 (78.48	5.72 5.69	12.22 12.11)	3440-3384 (NH_2, NH), 1608 (C=N)		
7	155 Methanol	60	$C_{20}H_{14}NCl$ (303.777)	79.07 (79.00	4.65 4.55	4.61 4.59)	3320 (NH)		
8	70 benzene	70	$C_{20}H_{15}N_2Cl$ (318.793)	75.35 (75.28	4.74 4.67	8.79 8.69)	3460-3320 (NH_2, NH)		
9	150 benzene	75	$C_{27}H_{18}N_2O$ (386.43)	83.91 (83.89	4.70 4.55	7.25 7.15)	3391 (NH), 1600 (C=N)	386 (Mol. wt)	8.2 (s, 1H, CH=N), 8.1-6.49 (m, 16 Ph, Hs)
10	above 200 Acetone	60	$C_{22}H_{17}N_3$ (323.38)	81.71 (81.69	5.30 5.25	13.00 12.90)	3372 (NH), 1604 (C=N)	323.4 (Mol. wt)	
11	above 250 acetone	50	$C_{23}H_{19}N_3S$ (369.46)	74.76 (74.69	5.18 5.09	11.37 11.29)	3356 (NH, 1640 (C=N)	355 (Mol. wt −S), 326 (Mol. wt − S − C_2H_5), 312 (Mol. wt − S − C_2H_5 − N)	
12	above 250 acetone	60	$C_{26}H_{18}N_2O$ (374.42)	83.40 (83.35	4.85 4.75	7.48 7.39)	3397 (broad NH)	374.3 (Mol. wt)	

dec. = decomposition. Cl and S analysis: **7**: Cl, 11.67 (11.60); **8**: Cl, 11.12 (11.00); **11**: S, 8.68 (8.55).

Table II-Anti-inflammatory activity of indomethacin and the tested compounds compared with control positive group

Compd	30 min		60 min		90 min		120 min	
Control +ve	A	100.4 ± 2.1	A	106.8 ± 3.1	AC	118.74 ± 5.8	AC	122.32 ± 6.32
1a	D	129.17 ± 7.79	BC	101 ± 2.12	B	97.3 ± 3.13	B	67 ± 4.53
1b	A	113.83 ± 6.93	A	75.3 ± 1.94	A	72.83 ± 3.70	AC	96.7 ± 5.58
3	B	63 ± 2.76	A	70 ± 2.89	A	72.3 ± 2.12	B	72 ± 2.05
4	CE	101.7 ± 2.4	A	74.2 ± 2.79	BC	105.8 ± 2.98	A	100.7 ± 3.45
5a	B	72 ± 1.37	A	74.33 ± 1.65	B	97.3 ± 2.6	AC	96.2 ± 1.66
5b	AC	103.2 ± 4.09	C	110.5 ± 5.56	C	198.83 ± 5.66	A	98.3 ± 3.07
6a	B	73.2 ± 3.9	A	71 ± 3.54	A	72.7 ± 2.1	A	98.3 ± 1.69
6b	CE	99.3 ± 1.98	B	97.83 ± 1.8	B	97 ± 2.45	A	98.3 ± 3.33
Indomethacin	E	91.17 ± 3.27	A	77.17 ± 1.70	A	83.17 ± 3.66	C	86 ± 3.43

A, B, C, D, E, F: Means in each row not showing a common letter differ significantly ($P<0.05$).

using analysis variance and least significant difference test[14] (cf. Table II).

Compounds **1a, b** had acute antiinflammatory effect. Substitution of **1b** in position-6 by a semicarbazone group i.e. compound **3** improved the antiinflammatory activity through acute action. Compound **3** was more potent than indomethacin. Unfortunately cyclization of **3** with ferric chloride to obtain **4** abolished the effect.

Chalcone **5a** showed an acute antiinflammatory effect while no effect was observed in the case of **5b**.

The pyrazoline derivative **6a** possesses an acute antiinflammatory activity while compound **6b** does show any activity.

It is important to note that compounds **1a** and **3** were the most potent antiinflammatory compounds in comparison to indomethacin.

Analgesic activity

It was investigated using the hot plate method[15]. The tested compounds **1a, b; 3; 4; 5a, b; 6a, b** were given to mice at a dose level of 10 mg/kg.The mean reaction time of control, aspirin-treated mice and the tested compounds were calculated using analysis of variance and least significant difference (cf. Table III).

The starting material **1a** had significant analgesic effect resembling aspirin while the 5-methoxy derivatives **1a** had significant effect compared to aspirin. Condensation of **2a** with semicarbazide hydrochloride gave the schiff's base **3** which is more potent than aspirin. Cyclization with ferric chloride yielded compound **4** which did not show any analgesic activity.

Chalcone **5a** was devoid of any analgesic effect while **5b** had significant analgesic effect and was more potent than aspirin. The pyrazoline derivatives **6a, b** failed to show any analgesic effect.

Finally, we conclude that compounds **3** and **5** were potent compounds than aspirin due to the free methoxy in position-5, *ortho* to the unsaturated amide side chain. Moreover, compound **3** was the most potent antiinflammatory and analgesic compound compared to the positive control.

Experimental Section

All m.ps are uncorrected. The IR spectra were recorded in KBr on a Unicam SP 200 spectrophotometer and ^{1}H-NMR spectra in $CDCl_3$ or DMSO using a Geol DFF 100 (270 MHz) with TMS as an internal reference.

2, 3-Diphenylindole-6-carboxaldehyde derivatives 2a, b[16]. Phosphorous oxychloride (2 mL) was added to 1a, b (0.01 mole) in DMF (20 mL). The mixture was refluxed for 4 hr, decomposed with saturated solution of hydrated sodium acetate and filtered.

Preparation of the semicarbazone 3b. A diluted ethanolic solution (1:1) of semicarbazide hydrochloride (0.02 mole) was added to an ethanolic solution of **2b** (0.02 mole) in ethanol (20 mL). The mixture was acidified with acetic acid (0.5 mL) dropwise at room temperature with stirring for 2 hr. The precipitate obtained was collected and washed with water and crystallized.

Cyclization of the semicarbazone 3b. Preparation of 4b. An ethanolic solution of ferric chloride hexahydrate (2 moles, 10 mL) was added to a solution of semicarbazone **3b** (0.01 mole) in ethanol (30 mL). The mixture was heated at 150°C for few min and filtered after 24 hr. The solid so obtained was washed and crystallized.

Table III—Analgesic effect of tested compounds at one dose level as compared to control and aspirine treated groups of mature mice (n = 5 mice) in seconds

Time*/gr	15 min		30 min		45 min		60 min		75 min		90 min	
Control	AD	15.87 ±0.78	A	11.27 ±0.45	A	11.57 ±0.398	A	12.5 ±0.43	AE	11.67 ±0.49	AB	12.45 ±0.61
1b	A	13.08 ±0.6	BE	20.25 ±0.77	B	17.75 ±0.63	BD	19.7 ±0.88	BC	18.7 ±0.88	B	11.8 ±0.53
1a	AD	15.5 ±0.76	BF	21.8 ±1.17	BD	19.97 0.83	B	20.91 ±0.92	CH	21.17 ±1.08	C	20.7 ±0.88
3	C	22.3 ±1.34	C	49.95 ±2.11	C	25.3 ±1.23	AC	14.83 ±0.70	BDE	16.2 ±1.08	E	17.5 ±0.99
4	A	13.17 ±0.95	DE	17.5 ±0.56	D	15.7 ±0.67	DC	17.83 ±0.48	AFG	13.0 ±0.58	AB D	13.7 ±0.56
5a	A	13.5 ±0.85	D	16.0 ±0.68	AD	12.83 ±0.97	AC	15.3 ±0.84	DEG	15.0 ±0.82	ADE	15.2 ±0.79
5b	B	35.83 ±2.02	C	47.45 ±2.56	C	26.17 ±0.87	C	16.0 ±0.93	DF	15.33 ±0.99	DE	16.42 ±1.13
6a	A	14.0 ±0.58	D	15.5 ±1.02	AD	15.0 ±0.93	CE	16.5 ±0.75	BDE	16.5 ±0.72	ADE	14.7 ±0.88
6b	A	13.17 ±0.83	D	16.7 ±0.71	D	15.5 ±0.85	AC	13.3 ±0.67	EF	14.5 ±0.67	ABD	14.5 ±0.56

Sample "F" = 131.0586, Column = 120.1758, Interaction = 41.82549. *P* value 2E-89, 5E-57, 5E-86. F crit. = 1.917449, 2.407752, 1.464418.

A, B, C, D, E, F: Means in each row not showing a common letter differ significantly ($P < 0.05$).

*The time in the first raw of the table is the time of administration by minutes, while the figures in the table explained the time of reaction on the hot plate by seconds.

Preparation of chalcones 5a, b. To a solution of **2** (0.01 mole) in ethanol (20 mL), *p*-aminoacetophenone (0.01 mole) and 10% NaOH (10 mL) were added and the mixture was stirred for 1 hr. The reaction mixture was refluxed for 3 hr, and neutralized with dil. HCl. The residue was filtered off and crystallized.

Cyclization of chalcone 5a, b: Preparation of 6a, b. To a solution of **5** (0.03 mole) in methanol (20 mL), an excess of hydrazine hydrate was added. The reaction mixture was refluxed for 3 hr and the precipitate formed was filtered off and crystallized.

Preparation of 2,3-diphenyl-5-chloro-1*H*-indole 7[17]. *p*-Chloroaniline hydrochloride (0.03 mole) was fused with benzoin (0.03 mole). The reaction mixture was acidified with conc. HCl and the solid so obtained was crystallized.

Preparation of compound 8. A mixture of conc. nitric and conc. sulphuric acid (1:1, 10 mL) was added to **7** (1 gm, 0.003 mole) in portion of 2-3 ml during about 15 min, the reaction mixture was shaken vigorously and the temperature not allowed to raise above 60°C. The reaction was heated on a boiling water-bath for 30 min, cooled to room temperature and poured into 200 mL of cold water. The nitro compound was filtered and washed well with cold water. Conc. HCl (10 mL) was added in small portions to a mixture of nitro compound (1 g, 0.0028 mole) and granulated in (3 g). The mixture was shaken vigorously and heated under reflux at 100°C for about 1 hr. The mixture was then cooled and made alkaline with 40% NaOH solution. The precipitate formed was filtered off and crystallized.

Preparation of compound 9. A mixture of compound **8** (0.003 mole) and salicylaldehyde (1 mL) was refluxed in dry benzene or pyridine (25 mL) for 4 hr on a water-bath. The precipitate formed was filtered off and crystallized.

Preparation of compounds 10 and 12. Acetonitrile or *o*-chlorophenol (3 mL) was added slowly to a solution of **8** (0.01 mole) in dry DMF (50 ml). The reaction mixture was refluxed for 1 hr and left to cool. To the product so obtained was added sodium hydride (1 g), and the reaction mixture was refluxed for 1 hr and left to cool. The reaction mixture was then treated with iced water and the precipitate formed was filtered off and crystallized.

Preparation of compound 11. To a solution of **8** (0.01 mole) in tetrahydrofuran (12 mL), ethyl isothiocyanate (2 mole) was added dropwise at room temp. with stirring for 2 hr. The reaction mixture was left for 3 days and the carbamate obtained was cyclized by dissolving in dry DMF and adding sodium hydride (1 g). The reaction mixture was refluxed for 1 hr, left to cool and treated with iced water. The precipitate obtained was washed with water and crystallized.

References

1 Harendza-Harinxma A J, *US Pat*, 4,847,283 (1989); *Chem Abstr*, 112, **1990**, 11944t.
2 Szmuszkovicz J, (Upjohn Co.), *US Pat* 3,654,308 (1972); *Chem Abstr*, 77, **1972**, 34319r.
3 Welstead W J & Stauffer H F, *Ger Offen*, 2,324,793 (1973); *Chem Abstr*, 80, **1974**, 47836u.
4 Gadaginamath G S & Joshi R G, *Indian J Chem*, 34B, **1995**, 120.
5 Jag Mohan & Singh V, *Indian J Chem*, 34B, **1995**, 125.
6 Agarwal A & Agarwal S K, *Indian J Chem*, 34B, **1995**, 323.
7 Purohit M G, Badiger G R & Kalaskar, *Indian J Chem*, 34B, **1995**, 746.
8 Tiwari S, Tiwari N, Agarwal T, Khan M H & Nizamuddin, *Indian J Chem*, 34B, **1995**, 5010.
9 Shyadligeri A S & Gadaginamath G S, *Indian J Chem*, 34B, **1995**, 1059.
10 Osford A W, Butina D & Owen M R (Glaxo Group Ltd), *Eur Pat Appl Ep* (1989) 303, 507; *Chem Abstr*, 111, **1989**, 57535t.
11 Lundt B F & Anderson W, *Ger Offen*, 2,024,966 (1970); *Chem Abstr*, 74, **1971**, 53520d.
12 Hishmat O. H, El-Shabrawy O A, Nakkady S S & Mahmoud S S, *Egypt J Pharm Sci*, 31, **1990**, 219.
13 Winter C A, Risley E A & Nuss G W, *Proc Soc Exp Biol Med*, 111, **1962**, 544.
14 *Statistical methods*, edited by W G Snedecor & G W Cochran (Iowa State University Press, Ames, Iowa), **1971**.
15 Jansen P A J & Jageneau A H, *J Pharm Pharmacol*, 9, **1957**, 381.
16 Hans J T & Karl S, *Chem Ber*, 91, **1958**, 2089.
17 Ockenden D W & Schofield K, *J Chem Soc*, 51, **1957**, 3175.