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Synthesis and Biological Activities of New Substituted Indoles

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Abstract □ 2,3-Diphenyl-6-formyl-5-methoxyindole reacts with ethyl cyano acetate to yield the arylidene derivative which forms with urea and thiourea the corresponding pyrimidine derivatives. The arylidene derivatives react with hydrazines and with active methylenes to form the respective pyrazole derivatives and the α, β-disubstituted acrylonitriles. Seven new compounds were tested for their effects on the arterial blood pressure of rats and analgesic activity.

Keywords □ /Indolyl pyrimidines, acrylonitriles, analgesics, arterial blood pressure effects.

It is well known that the pyrimidine ring occurs in a great variety of substances which play a vital role in biological processes. Moreover, the biological activities of pyrazoles have stimulated considerable research in this field[1,2]. In addition, indole derivatives possess pronounced biological properties[3-6]. The newly synthesized indolyl pyrimidines and indolyl pyrazoles are interesting candidates for biological studies.

EXPERIMENTAL

2,3-Diphenyl-6-formyl-5-methoxyindole **2** was prepared by the formylation of 2,3-diphenyl-5-methoxyindole **1**[7]. Compound **2** reacts with ethyl cyanoacetate to form the corresponding arylidene derivative **3**.

The ^{1}H-NMR spectrum of **3** shows signals at δ 8.95 (1H, acrylic proton s), δ 8.85 (1H, NH, broad s), δ 8.6 (1H, H-4, s) δ 7.3-7.5 (10H, aromatic protons, m) δ 7.05 (1H, H-7, s), δ 4.35-4.45 (2H, CH_2, q), δ 3.85 (3H, OCH_3, s) and δ 1.35-1.45 (3H, CH_3, t). Its IR spectrum is given in Table I.

When **3** was treated with urea in the presence of potassium carbonate, the corresponding 5-cyano-6-substituted-2,4-dioxo-1,2,3,4-tetrahydro-pyrimidine **4** was obtained. (IR, cf. Table I).

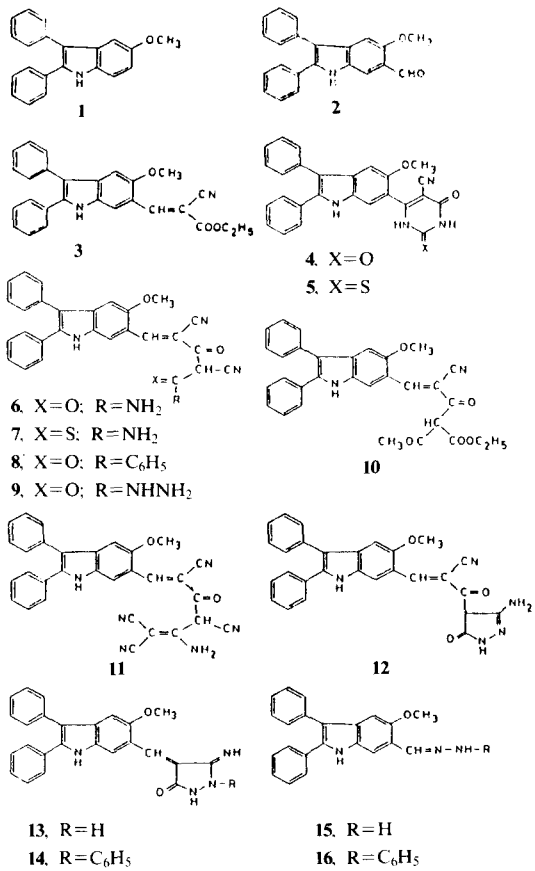
On the other hand, **3** reacts with thiourea in the presence of potassium carbonate to form 5-cyano-6-(2′,3′-diphenyl-5′-methoxy-6′-indolyl)-4-oxo-2-thioxo-1,2,3,4-tetrahydro-pyrimidine **5**.

The cinnamate derivative **3** reacts with active methylene compounds, *i.e.* cyanoacetamide, thiocyanoacetamide, ω-cyanoacetophenone and cyanoacetic acid hydrazine, to form the corresponding α, β-disubstituted acrylonitrile derivatives **6-9** by loss of one molecule of ethanol. In a similar manner, the cinnamate derivative **3** forms the corresponding disubstituted acrylonitriles **10**, **11** and **12** by reaction with ethylacetoacetate, malononitriledimer and 3-amino-2-pyrazoline-5-one, respectively.

The ^{1}H-NMR of compound **9** shows signals at δ 8.6 (1H, NH, broad s), δ 8.5 (1H, acrylic protons, s) δ 7.9 (1H, H-4, s), δ 7.2-7.5 (10H, phenyl protons, m), δ 6.9 (1H, H-7, s), δ 4.2 (1H, CH-methine, s), δ 3.8 (3H, OCH_3, s) and δ 0.9-1.2 (3H, $NHNH_2$, m). The IR spectra of compounds 6, 8, 9 and 12 are given in Table I.

To explore the formation of some new indolyl pyrazole derivatives, the behaviour of ethyl α-cyano-β-substituted cinamate **3** towards hydrazine hydrate and phenyl hydrazine in ethanol to yield the corresponding pyrazolone derivatives **13**, **14**, respectively.

In order to exclude the possibility of the formation of the hydrazones of 2,3-diphenyl-6-formyl-5-



methoxy **2** was reacted with hydrazine hydrate and phenyl hydrazine in alcohol to yield the hydrazone and the phenyl hydrazone **15**, **16**, respectively. Mixed melting points with the corresponding pyrazolone and phenyl pyrazolone derivatives gave a depression, thus proving that no fission of the cinnamate group occured. The IR spectra of compounds **13-16** are shown in Table I.

All melting points are uncorrected. The infrared spectra were recorded (KBr) on a Unicam SP-2000 spectrophotometer. ^{1}H-NMR (at 100 MHz) were obtained in $CDCl_3$ with a DFT 100, F. A. Jeal, Tokyo, using $SiMe_4$ as internal standard. Microanalytical data were performed by the Microanalytical Laboratory at the National Research Centre, Cairo-Dokki. The compounds were analyzed for C, H and N, compounds **5** and **7** also for, S, the results being within ± 0.4% of the theoretical values.

2,3-Diphenyl-6-formly-5-methoxyindole, 2

To 3 g of 2,3-diphenyl-5-methoxyindole **1**[7] dissolved in 10 m*l* of dimethyl formamide, 7 m*l* of phosphorous oxychloride were added and the mixture was heated on a water bath for two hours. A saturated solution of sodium acetate was added to the cold reaction mixture and left overnight. The precipitate was filtered, washed and crystallized from toluene as yellowish crystals (see Table I).

Ethyl α-cyano-β-(2,3-diphenyl-5-methoxy-6-indolyl) cinnamate, 3

A mixture of 1.6 g of **2**, 0.4 g of ethyl cyanoacetate in 20 m*l* of ethanol and 2 drops of triethylamine was well stirred at room temperature for 3 hours. The solid so obtained was filtered and crystallized from ethanol as orange crystals.

5-Cyano-6-(2',3'-diphenyl-5'-methoxy-6'-indolyl)-2,4-dioxo-1,2,3,4-tetrahydropyrimidine, 4

A mixture of 4 g of **3**, 1 g of potassium carbonate and 1 g of urea in 20 m*l* of ethanol was refluxed for 5 hours. The potassium salt of **4** which precipitated was filtered off, washed with very little ethanol and dissolved in hot water, left to cool and acidified with acetic acid while stirring for 30 minutes. The product formed was filtered and crystallized from ethanol as greenish grey crystals.

5-Cyano-6-(2',3'-diphenyl-5'-methoxy-6'-indolyl)-4-oxo-2-thioxo-1,2,3,4-tetrahydropyrimidine, 5

Compound **5** was prepared in a manner similar to that used for **4**, using thiourea instead of urea and obtained as orange crystal from ethanol.

Preparation of α, β-disubstituted acrylonitrile derivatives 6-9 and the disubstituted acrylonitrile compounds 10, 11

General Procedure: A mixture of 2 g of **3** and 0.5 g of the active methylene compounds were refluxed in 40 m*l* ethanol and 2 drops of triethylamine. The solid that crystallized was collected and recrystallized. Compounds **6-9** and **11** were crystallized from benzene. Compounds **10** and **12** were crystallized from ethanol. All the acrylonitrile derivatives were separated as yellow to orange crystals, except **7** that was reddish in colour.

4-(2',3'-Diphenyl-5'-methoxy-6'-indolylidene)-3-amino-2-pyrazolin-5-one, 13 and 4-(2,3-diphenyl-5-methoxy-6-indolylidene) 3-imino-2-phenylpyrazol-5-one, 14

Table I. Physical and spectral data

Compound No	IR NH/CH	IR CN	IR C=O	IR C=C/C=N	M.P ℃	Yield %	Molecular Formula	Molecular Weight
2	3375		1665	1600	190	60	$C_{22}H_{17}NO_2$	327
3	3400	2200	1735	1600, 1590	206	70	$C_{27}H_{22}N_2O_3$	422
4	3600-3080 broad	2210	1720, 1705	1600	210	52	$C_{26}H_{18}N_4O_3$	434
5					170	43	$C_{26}H_{16}N_4O_2S$	450
6	3370	2265, 2210	2670, 1690	1625, 1565	180-181	70	$C_{28}H_{20}N_4O_3$	460
7					275	60	$C_{28}H_{20}N_4O_2S$	483
8	3420, 3300	2260	1700, 1655	1600	165	80	$C_{34}H_{23}N_3O_3$	521
9	3320	2260	1685, 1675	1625, 1600	230	80	$C_{28}H_{21}N_5O_3$	475
10					165-170	70	$C_{31}H_{26}N_2O_5$	506
11					180	70	$C_{31}H_{20}N_6O_2$	508
12	3385, 3350	2250	1740, 1700	1625, 1570	240	80	$C_{28}H_{21}N5O_3$	475
13	3370, 3200		1680	1640	168	80	$C_{25}H_{20}N_4O_2$	408
14	3320, 3200		1690	1620	225	70	$C_{31}H_{24}N_4O_2$	484
15	3320			1640	190	80	$C_{22}H_{19}N_3O$	341
16	3320			1640	200	80	$C_{28}H_{23}N_{30}$	417

To a solution of 0.5 g of **3** in 20 m*l* of ethanol hydrazine hydrate or phenyl hydrazine 0.5 m*l* was added. The mixture was refluxed for two hours, then left to cool, filtered and the solid so obtained was crystallized from ethanol. Compound **13** was separated as yellowish crystals. Compound **14** was separated as whitish crystals.

Hydrazone, 15 and phenyl hydrazone, 16 of 2,3-diphenyl-6-formyl-5-methoxyindole

A mixture of 0.5 g of **2** in 20 m*l* ethanol and 0.5 m*l* of hydrazine hydrate or phenyl hydrazine was refluxed for two hours on a water bath. The product was filtered and crystallized from ethanol, as yellowish crystals.

Many indole derivatives have been shown to produce hypotensive and analgesic effects[8], therefore it became of interest to test the newly synthesized compounds **3**, **6-10** and **12** for their possible effects on the arterial blood pressure and analgesia in rats and mice, respectively.

The method of Mcleod *et al.*[9] was used, in which rats (150-200 gm) were anaesthetized by urethane, the trachea, one common carotid artery and the femoral vein were canulated using special canulas. The common carotid artery was connected to a special transducer, which was connected to a Harvard 2120 biographic recorder. Rats were heparinized by intravenous injection of heparin. The tested compounds were injected into the femoral vein after being completely dissolved in a solution of propylene glycol in distilled water (25%), then were washed with 0.2 m*l* saline.

Table II. Effect of the tested compounds on the systolic blood pressure of anaesthetized rats

Dose in mg/kg body. wt.	Decrease % Compounds **6**	**12**	**7**	**10**	**9**	**8**	**3**
0.25	No	T	T	6	4	No	T
0.50	No	T	32	14	11	No	T
0.75	No	11	38	24	17	No	13

Tested compounds and propylene glycol were administered and the blood pressure was recorded before and five minutes after administration. Each dose was tested 3-5 times and the mean percentage effect was calculated.

Analgesic effect of the tested compounds

The analgesic effect was investigated for the tested compounds using the method described by Janssen and Jageneu[10]. The reaction time was taken as the interval from the instance the mouse reaches the hot plate until it licks its feet or jumps out of the cylinder. Mice were divided into groups of 6-8 animals. The tested compounds dissolved in a solution

Table III. The analgesic effect of the tested compounds and paracetamol (500 mg/kg body weight)

Time in minutes	Mean reaction time in seconds+S.E. Tested compounds								
	Prop.glyc.	**6**	**12**	**7**	**10**	**9**	**8**	**3**	Paracetamol
10	12.2 +0.45	9.8 0.50	10.4 0.67	25.80** 2.20	25.40** 2.30	12 1.41	10 0.63	21.80** 1.15	17.2** 0.86
20	12.8 0.58	20.40** 1.33	19.80** 1.10	22** 1.60	24.80** 0.48	13.4 1.16	10 0.67	22.20** 1.06	26 ** 1
30	11.6 1.02	21.80** 1.39	17.80** 0.86	20.40** 1.40	23.80** 1.90	10.80 0.86	13.2 1.03	18.80** 0.66	23.4** 0.81
45	13.2 0.80	20.80** 1.31	20.40** 1.90	20.20** 2.30	25.20** 2.5	15 0.83	11.80 0.33	12.40 0.74	23.4** 0.97
60	12 0.89	18.60** 2	20.40** 2.11	27.8** 1.2	24.60** 0.51	12 0.54	11.2 0.76	14.2** 1.35	23.20** 1.06
120	12.8 1.01	18.60* 1.90	20.40** 1.30	21** 1.30	21.40** 1.50	11.6 0.67	11.60 0.96	13 0.83	20.40** 0.92

of propylene glycol in distilled water (25%) and paracetamol were orally administered to animals in 500 mg/kg dose. A control group was given 25% propylene glycol in distilled water. The reaction time was taken after 10, 20, 30, 45, 60 and 120 minutes after oral administration of the tested compounds.

RESULTS

Table II shows the effect of the tested compounds **3**, **6-10** and **12** on the blood pressure of rats. Five out of the seven tested compounds showed a lowering effect on the arterial blood pressure of rats, they were **7**, **10**, **9**, **3** and **12** in a decreasing order. Compounds **6** and **8** failed to demonstrate any effect on the arterial blood pressure of rats in the tested doses mentioned.

Table III shows the analgesic effect of the tested compounds **3**, **6-10** and **12** in comparison to paracetamol. Compounds **10**, **7**, **12**, **6** and **3** were found to be active in decreasing order. On the other hand compounds **8** and **9** were found to be inactive in the tested doses mentioned.

DISCUSSION

It was observed that the introduction of ethyl acetoacetate, thiocyanocetamide, 3-amino-2-pyrazoline-5-one and cyanoacetamide groups in compounds **10**, **7**, **12** and **6** to the starting compound **3** increased the duration of action of the tested compounds, while introducing ω-cyanoacetophenone and cyanoacetic acid hydrazide, in compounds **8** and **9** abolished the analgesic activity.

The starting compound **3** showed a significant analgesic activity of short duration of action and a lowering effect on the arterial blood pressure with high dose. Further substitution by introduction of the above mentioned groups in compounds **10**, **7**, **12** and **6** to the starting compound resulted in the preservation and even increase of the biological activity.

Compounds **9**, **10** and **7** showed lowering effect on both the blood pressure and analgesic effects, respectively, while they failed to demonstrate any other effects, which might be due to sub-effective doses used. Compounds **8** and **6** failed to demonstrate any biological activity in the doses used, this might be due to the introduction of the bulky phenyl residue in the molecule. Moreover, the activity of compound **7** was found to be higher than that of **6** due to the introduction of the sulphur atom.

LITERATURE CITED

1. Hori, M., Ito, E., Takita, T., Koyama, G., Takeuchi, T. and Umezawa, H.: A new antibiotic for-

mycin. *J. Antibiotics* (Tokyo), Ser. A. **17**, 96 (1964).
2. Kayama, G. and Umezawa, H.: Formycin B and its relation to Formycin. *J. Antibiotics* (Tokyo), Ser. A. **18**, 175 (1965).
3. Szmuszkovicz, J.: Antiinflammatory, antipyretic and analgesic trifluoromethyl substituted 2,3-bis (p-methoxyphenyl) indoles. U. S. 3,551,451 (Cl. 260.326.16; (07d), 29 Dec. 1970, Appli. 26 May (1967); 4 pp.
4. Szmuszkovicz, J.: Antiinflammatory 5-alkonyl-2, 3-bis (p-methoxyphenyl) indoles. U. S. 3,565,912 (Cl. 260-326.16; (07d), 23 Feb. 1971. Appl. 27 Jan. (1969); 8 pp.
5. Szmuszkovicz, J.: Antiinflammatory 2,3-bis (p-methoxyphenyl) indole 5-carboxylic acid derivatives. U. S. 3,654,308 (Cl. 260-326. 13R; (07d) 04 Apr. 1972. Appl. 479,402,27 Jan (1968); 8 pp.
6. Whitehead, C. W. and Whitesitt, C. A.: Effect of lipophilic substituents on some biological properties of indoles. *J. Med. Chem.* **17**, 1298 (1974).
7. Ockenden, D. W. and Schoffied, K.: Indoles part III. The action of (A) ozone and (B) osmium tetroxide on some indole derivatives. *J. Chem. Soc.* 612 (1953).
8. Lundt, B. F., and Anderson, W.: Analgesic 3-(aminoalkoxy) indoles. *Ger. Offen.* 2,024,966 (Cl. C. 07d), 03 Dec. 1970, *Brit. Appl.* 27 (1969), 42 pp.
9. Mcleod, L. J.: "*Pharmacological experiments on intact preparations*", E & S, Livingstone Edindurgh and London (1970).
10. Jansen, P. A. J. and Jageneau, A. H.: "Series of potent analgesics -d-2,2-diphenyhl-3-methyl-4-morpholino butyl pyrolidine and related basic amides. (II) Comparative analgesic activity, acute toxicity and tolerance development in rats for R, 875, morphine, pethidine and methadone", *J. Pharm. Pharmac.* **9**, 381 (1957).